Product Description
SALSA® MLPA® Probemix P101-B4 STK11

To be used with the MLPA General Protocol.

Version B4
For complete product history see page 9.

Catalogue numbers:
- **P101-025R:** SALSA MLPA Probemix P101 STK11, 25 reactions.
- **P101-050R:** SALSA MLPA Probemix P101 STK11, 50 reactions.
- **P101-100R:** SALSA MLPA Probemix P101 STK11, 100 reactions.

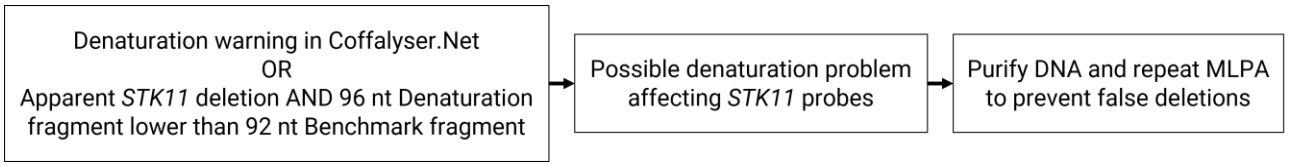
To be used in combination with a SALSA MLPA reagent kit and Coffalyser.Net data analysis software. MLPA reagent kits are either provided with FAM or Cy5.0 dye-labelled PCR primer, suitable for Applied Biosystems and Beckman/SCIEX capillary sequencers, respectively (see www.mrcholland.com).

Certificate of Analysis
Information regarding storage conditions, quality tests, and a sample electropherogram from the current sales lot is available at www.mrcholland.com.

Precautions and warnings
For professional use only. Always consult the most recent product description AND the MLPA General Protocol before use: www.mrcholland.com. It is the responsibility of the user to be aware of the latest scientific knowledge of the application before drawing any conclusions from findings generated with this product.

Extra instructions for SALSA MLPA Probemix P101 STK11 in order to prevent false positive STK11 deletions

Visual denaturation check in case of apparent *STK11* deletions: The *STK11* gene region is (one of) the hardest-to-denature genes known due to an extreme high GC content. Impaired sample denaturation, for instance due to a high salt concentration, can inhibit probe-to-sample binding, thereby causing MLPA probe signals to be reduced. In most cases, these denaturation problems will be successfully identified and warned for by Coffalyser.Net software. **However, at certain salt concentrations (around 15-30 mM) *STK11* probes, in particular the last exons of *STK11*, may be affected by incomplete denaturation without the software issuing a warning! Therefore, an additional visual check of the 96 nt Denaturation fragment needs to be performed by the user; in case of denaturation problems, the DNA sample needs to be diluted or purified and the MLPA reaction repeated to prevent false positive results.**



Context: Usually Coffalyser.Net issues a sample denaturation warning when the 88 nt and/or 96 nt Denaturation fragments are too low. However, as the *STK11* gene is more difficult to denature than other gene regions, **an additional visual check is needed when interpreting the results**. In case of apparent (partial) deletions, the 96 nt Denaturation fragment should be visually examined, as this control fragment is most sensitive to denaturation problems. When the 96 nt Denaturation fragment is lower than the 92 nt Benchmark fragment (In Coffalyser.Net, open *Samples results explorer*; if D2-fragment(s) ratio < 1.00) the sample is likely affected by a poor denaturation.

Dilution and purification instructions: If DNA quantity allows for this the sample DNA can be diluted with $TE_{0.1}$ (MLPA General Protocol) to reduce salt concentrations and the MLPA experiment be repeated. If this

does not resolve the issue, the use of an additional purification step or an alternative DNA extraction method may resolve cases with high salt concentrations. When using silica column-based DNA purification, salt concentrations can often be reduced by inclusion of a wash step with 85% ethanol before the elution step.

Intended purpose

The SALSA MLPA probemix P101 STK11 is an in vitro diagnostic (IVD)[1] or research use only (RUO) semi-quantitative assay[2] for the detection of deletions or duplications in the human *STK11* gene in genomic DNA isolated from human peripheral whole blood specimens. P101 STK11 is intended to confirm a potential cause of and clinical diagnosis for Peutz-Jeghers syndrome and for molecular genetic testing of at-risk family members.

Copy number variations (CNVs) detected with P101 STK11 probemix should be confirmed by another technique. In particular, CNVs detected by only a single probe always require confirmation by another method. Most defects in the *STK11* gene are point mutations, none of which will be detected by MLPA. It is therefore recommended to use this assay in combination with sequence analysis.

Assay results are intended to be used in conjunction with other clinical and diagnostic findings, consistent with professional standards of practice, including confirmation by alternative methods, clinical genetic evaluation, and counselling, as appropriate. The results of this test should be interpreted by a clinical molecular geneticist or equivalent.

This device is not intended to be used for standalone diagnostic purposes, pre-implantation or prenatal testing, population screening, or for the detection of, or screening for, acquired or somatic genetic aberrations, e.g from DNA extracted from formalin-fixed paraffin embedded (FFPE) or fresh tumour materials.

[1]Please note that this probemix is for In Vitro Diagnostic use (IVD) in the countries specified at the end of the product description. In all other countries, the product is for Research Use Only (RUO).

[2]To be used in combination with a SALSA MLPA Reagent Kit and Coffalyser.Net analysis software.

Clinical background

Peutz-Jeghers syndrome (PJS) is an autosomal dominant disorder characterized by benign gastrointestinal polyps, hyper-pigmented skin spots, and an increased risk (>15x) of malignant epithelial cancers at various anatomic sites (colorectal, gastric, pancreatic, breast, uterine cervix, and ovarian cancers). The prevalence of this condition is uncertain; estimates range from 1 in 25.000 to 300.000 individuals. The age of onset of symptoms from polyps is variable, with some children developing symptoms within the first few years of life. About one-third of patients with PJS are diagnosed before the age of 10 years and up to 60% of the cases develop their first clinical manifestations before the age of 30 years. The basis of familial PJS is a germline mutation in the *STK11* tumour suppressor gene, located in chromosomal region 19p13.3.

STK11 alterations in PJS patients comprise mainly point mutations and it is estimated that ~15-20% of pathogenic mutations in the *STK11* gene are attributed to large deletions/duplications, which is comparable between PJS populations (Borun et al. 2015, Chow et al. 2006, Orellana et al. 2013). The *STK11* gene is frequently inactivated by deletions or by point mutations in several cancer types, including lung and cervical cancer, and inactivation is suggested to be associated with disease progression (Ji et al. 2007, Wingo et al. 2009).

More information is available at https://www.ncbi.nlm.nih.gov/books/NBK1266/.

Gene structure

The *STK11* gene spans 23 kilobases (kb) on chromosome 19p13.3 and contains 10 exons. The *STK11* LRG_319 is available at www.lrg-sequence.org and is identical to GenBank NG_007460.2.

Transcript variants

For *STK11,* one transcript variant has been described encoding the full length protein (NM_000455.5; 3293 nt; coding sequence 1137-2438; http://www.ncbi.nlm.nih.gov/gene/6794). This sequence is a reference

standard in the NCBI RefSeq project. The ATG translation start site is located in exon 1 and the stop codon is located in exon 9.

Exon numbering
The *STK11* exon numbering used in this P101-B4 STK11 product description is the exon numbering from the LRG_319 sequence. The exon numbering of the NM_ sequence that was used for determining a probe's ligation site does not always correspond to the exon numbering obtained from the LRG sequences. As changes to the databases can occur after release of this product description, the NM_ sequence and exon numbering may not be up-to-date.

Probemix content
The SALSA MLPA Probemix P101-B4 STK11 contains 27 MLPA probes with amplification products between 150 and 391 nucleotides (nt). This includes 12 probes for the *STK11* gene (one probe for each exon and three probes for exon 1), 3 probes for genes located upstream of *STK11*, and 2 DNA denaturation probes. In addition, 10 reference probes are included that detect autosomal chromosomal locations. Complete probe sequences and the identity of the genes detected by the reference probes are available online (www.mrcholland.com).

This probemix contains nine quality control fragments generating amplification products between 64 and 105 nt: four DNA Quantity fragments (Q-fragments), two DNA Denaturation fragments (D-fragments), one Benchmark fragment, and one chromosome X and one chromosome Y-specific fragment (see table below). More information on how to interpret observations on these control fragments can be found in the MLPA General Protocol and online at www.mrcholland.com.

Length (nt)	Name
64-70-76-82	Q-fragments (only visible with <100 ng sample DNA)
88-96	D-fragments (low signal indicates incomplete denaturation)
92	Benchmark fragment
100	X-fragment (X chromosome specific)
105	Y-fragment (Y chromosome specific)

MLPA technique
The principles of the MLPA technique (Schouten et al. 2002) are described in the MLPA General Protocol (www.mrcholland.com).

MLPA technique validation
Internal validation of the MLPA technique using 16 DNA samples from healthy individuals is required, in particular when using MLPA for the first time, or when changing the sample handling procedure, DNA extraction method or instruments used. This validation experiment should result in a standard deviation ≤0.10 for all probes over the experiment.

Required specimens
Extracted DNA from peripheral blood, free from impurities known to affect MLPA reactions. For more information please refer to the section on DNA sample treatment found in the MLPA General Protocol.

Reference samples
A sufficient number (≥3) of reference samples should be included in each MLPA experiment for data normalisation. All samples tested, including reference DNA samples, should be derived from the same tissue type, handled using the same procedure, and prepared using the same DNA extraction method when possible. Reference samples should be derived from different unrelated individuals who are from families without a history of Peutz-Jeghers syndrome. More information regarding the selection and use of reference samples can be found in the MLPA General Protocol (www.mrcholland.com).

Positive control DNA samples
MRC Holland cannot provide positive DNA samples. Inclusion of a positive sample in each experiment is recommended. Coriell Institute (https://catalog.coriell.org) and Leibniz Institute DSMZ (https://www.dsmz.de/) have diverse collections of biological resources which may be used as positive control DNA samples in your MLPA experiments. The quality of cell lines can change; therefore samples should be validated before use.

Performance characteristics
The expected number of *STK11* deletions that can be detected with this MLPA probemix is ~15-20% of all mutations in patients with Peutz-Jeghers syndrome (Borun et al. 2015). The analytical sensitivity and specificity for the detection of deletions in *STK11* is very high and can be considered >99% (based on a 2005-2021 literature review).

Analytical performance can be compromised by: SNVs or other polymorphisms in the DNA target sequence, impurities in the DNA sample, incomplete DNA denaturation, the use of insufficient or too much sample DNA, the use of insufficient or unsuitable reference samples, problems with capillary electrophoresis or a poor data normalisation procedure and other technical errors. The MLPA General Protocol contains technical guidelines and information on data evaluation/normalisation.

Data analysis
Coffalyser.Net software should be used for data analysis in combination with the appropriate lot-specific MLPA Coffalyser sheet. For both, the latest version should be used. Coffalyser.Net software is freely downloadable at www.mrcholland.com. Use of other non-proprietary software may lead to inconclusive or false results. For more details on MLPA quality control and data analysis, including normalisation, see the Coffalyser.Net Reference Manual.

Interpretation of results
The expected results for the probes detecting autosomal sequences are allele copy numbers of 2 (normal), 1 (heterozygous deletion), or 3 (heterozygous duplication).

The standard deviation of each individual probe over all the reference samples should be ≤0.10 and the final ratio (FR) of each individual reference probe in the patient samples should be between 0.80 and 1.20. When these criteria are fulfilled, the following cut-off values for the FR of the probes can be used to interpret MLPA results for autosomal chromosomes or pseudo-autosomal regions:

Copy number status	Final ratio (FR)
Normal	0.80 < FR < 1.20
Homozygous deletion	FR = 0
Heterozygous deletion	0.40 < FR < 0.65
Heterozygous duplication	1.30 < FR < 1.65
Heterozygous triplication/homozygous duplication	1.75 < FR < 2.15
Ambiguous copy number	All other values

Note: The term “dosage quotient”, used in older product description versions, has been replaced by “final ratio” to become consistent with the terminology of the Coffalyser.Net software. (Calculations, cut-offs and interpretation remain unchanged.) Please note that the Coffalyser.Net software also shows arbitrary borders as part of the statistical analysis of results obtained in an experiment. As such, arbitrary borders are different from the final ratio cut-off values shown here above.

- Arranging probes according to chromosomal location facilitates interpretation of the results and may reveal more subtle changes such as those observed in mosaic cases. Analysis of parental samples may be necessary for correct interpretation of complex results.
- False positive results: Please note that abnormalities detected by a single probe (or multiple consecutive probes) still have a considerable chance of being a false positive result. Sequence changes (e.g. SNVs, point mutations) in the target sequence detected by a probe can be one cause. Incomplete DNA

denaturation (e.g. due to salt contamination) can also lead to decreased probe signals, in particular for probes located in or near a GC-rich region or in or near the *STK11* gene. The complete *STK11* gene is located in a very GC-rich region. The use of an additional purification step or an alternative DNA extraction method may resolve such cases. Additionally, contamination of DNA samples with cDNA or PCR amplicons of individual exons can lead to an increased probe signal (Varga et al. 2012). Analysis of an independently collected secondary DNA sample can exclude these kinds of contamination artefacts.

- Normal copy number variation in healthy individuals is described in the database of genomic variants: http://dgv.tcag.ca/dgv/app/home. Users should always consult the latest update of the database and scientific literature when interpreting their findings.
- Not all abnormalities detected by MLPA are pathogenic. In some genes, intragenic deletions are known that result in very mild or no disease (as described for *DMD* by Schwartz et al. 2007). For many genes, more than one transcript variant exists. Copy number changes of exons that are not present in all transcript variants may not have clinical significance. Duplications that include the first or last exon of a gene (e.g. exons 1-3) might not result in inactivation of that gene copy.
- Copy number changes detected by reference probes or flanking probes are unlikely to have any relation to the condition tested for.
- False results can be obtained if one or more peaks are off-scale. For example, a duplication of one or more exons can be obscured when peaks are off-scale, resulting in a false negative result. The risk on off-scale peaks is higher when probemixes are used that contain a relatively low number of probes. Coffalyser.Net software warns for off-scale peaks while other software does not. If one or more peaks are off-scale, rerun the PCR products using either: a lower injection voltage or a shorter injection time, or a reduced amount of sample by diluting PCR products.

P101 specific notes:

- This probemix is particularly prone to denaturation problems, see the box on page 1 and 2.
    - The use of DNA samples containing 15 mM or more salt can result in false positive deletion results due to incomplete denaturation.
    - A low signal of the 88 nt and 96 nt DNA denaturation control fragments provide a warning for incomplete DNA denaturation in Coffalyser.Net in case the sample contains 30 mM or more salt.
    - When the sample contains salt concentrations of ~15-30 mM, STK11 probes may show reduced probe signals even in the absence of a denaturation warning in the Coffalyser.Net software.
- Two extra probes at 159 nt and 178 nt located in GC-rich regions are present in this probemix. However, these probes are less salt sensitive and should therefore not be used to determine if denaturation was successful.
- One study suggests that 1–2 % of patients with clinical features of PJS could have a mosaic *STK11* mutation (McKay et al. 2015). In case of apparent mosaic *STK11* deletions, check for denaturation problems, see the box on page 1 and 2. Mosaic *STK11* deletions obtained with the P101 STK11 probemix must be confirmed by analysis of a second, independently collected DNA sample or a different technique, in order to exclude a false positive mosaic result.

Limitations of the procedure

- In most populations, the major cause of genetic defects in the *STK11* gene are small (point) mutations, none of which will be detected by using SALSA MLPA Probemix P101 STK11.
- MLPA cannot detect any changes that lie outside the target sequence of the probes and will not detect copy number neutral inversions or translocations. Even when MLPA did not detect any aberrations, the possibility remains that biological changes in that gene or chromosomal region *do* exist but remain undetected.
- Sequence changes (e.g. SNVs, point mutations) in the target sequence detected by a probe can cause false positive results. Mutations/SNVs (even when >20 nt from the probe ligation site) can reduce the probe signal by preventing ligation of the probe oligonucleotides or by destabilising the binding of a probe oligonucleotide to the sample DNA.
- The diagnostic use of P101 with DNA extracted from tumour tissue has not been validated.

Confirmation of results

Copy number changes detected by only a single probe always require confirmation by another method. An apparent deletion detected by a single probe can be due to e.g. a mutation/polymorphism that prevents ligation or destabilises the binding of probe oligonucleotides to the DNA sample. Sequence analysis can establish whether mutations or polymorphisms are present in the probe target sequence. The finding of a heterozygous mutation or polymorphism indicates that two different alleles of the sequence are present in the sample DNA and that a false positive MLPA result was obtained.

Copy number changes detected by more than one consecutive probe should be confirmed by another independent technique such as long range PCR, qPCR, array CGH or Southern blotting, whenever possible. Deletions/duplications of more than 50 kb in length can often be confirmed by FISH.

STK11 mutation database

http://databases.lovd.nl/shared/genes/STK11. We strongly encourage users to deposit positive results in the LOVD database. Recommendations for the nomenclature to describe deletions/duplications of one or more exons can be found on http://varnomen.hgvs.org/.

Please report copy number changes detected by the reference probes, false positive results due to SNVs and unusual results (e.g., a duplication of *STK11* exons 6 and 8 but not exon 7) to MRC Holland: info@mrcholland.com.

Table 1. SALSA MLPA Probemix P101-B4 STK11

Length (nt)	SALSA MLPA probe	Chromosomal position (hg18)[a]	
		Reference	*STK11*
64-105	Control fragments – see table in probemix content section for more information		
150	Reference probe 01171-L00616	8q	
159 »	DNA denaturation probe 05523-L04951	20q	
169 «	**STK11 probe** 03891-L03986		**Exon 10**
178 »	DNA denaturation probe 14170-L17280	22q	
184	Reference probe 13261-L14594	1p	
195 «	**STK11 probe** 03124-L03988		**Exon 1**
202 « ¬	Flanking probe 11955-L18080		19p13.3; 285 kb telomeric
214 ¬	Flanking probe 07916-L07646		19p13.3; 350 kb telomeric
221 «	**STK11 probe** 03125-L18081		**Exon 2**
229 «	**STK11 probe** 03126-L18082		**Exon 3**
238 «	**STK11 probe** 03127-L03338		**Exon 4**
247 «	**STK11 probe** 02215-L10041		**Exon 1**
256	Reference probe 02336-L01821	12q	
265 « ¬	Flanking probe 01737-L01313		19p13.3; 664 kb telomeric
274	Reference probe 02470-L01914	15q	
283 «	**STK11 probe** 16639-L19597		**Exon 5**
292 «	**STK11 probe** 03129-L03340		**Exon 6**
301	Reference probe 07636-L07321	10p	
310	Reference probe 15380-L17211	3p	
317 «	**STK11 probe** 16638-L19168		**Exon 7**
328	Reference probe 02663-L02130	11q	
337 «	**STK11 probe** 03131-L02583		**Exon 8**
346 « ±	**STK11 probe** 03132-L03990		**Exon 9**
355	Reference probe 15081-L16844	4q	
373 « ±	**STK11 probe** 02251-L10042		**Exon 1**
382	Reference probe 20537-L28127	1q	
391	Reference probe 17885-L22144	2p	

[a] See section Exon numbering on page 3 for more information.

± SNP rs372994361 strongly influences the 373 nt probe signal and has an allele frequency of more than 1:2500. SNP rs565993396 could influence the 346 nt probe signal. In case of apparent deletions, it is recommended to sequence the region targeted by this probe.
» Probe located in or near a GC-rich region. A low signal can be caused by salt contamination in the DNA sample, however, this probe is less salt sensitive as compared to the STK11 probes and should therefore not be used to determine if denaturation was successful.
« Probe located in or near a GC-rich region. A low signal can be caused by salt contamination in the DNA sample leading to incomplete DNA denaturation, especially of GC-rich regions. The use of DNA samples containing 15 mM or more salt can result in false positive *STK11* deletion results due to incomplete denaturation.
¬ Flanking probe. Included to help determine the extent of a deletion/duplication. Copy number alterations of only the flanking or reference probes are unlikely to be related to the condition tested.

SNVs located in the target sequence of a probe can influence probe hybridization and/or probe ligation. Please note: not all known SNVs are mentioned in the tables above. Single probe aberration(s) must be confirmed by another method.

Table 2. STK11 probes arranged according to chromosomal location

Length (nt)	SALSA MLPA probe	Gene exon[a]	Ligation site NM_000455.5	Partial sequence[b] (24 nt adjacent to ligation site)	Distance to next probe
265 « ¬	01737-L01313	*CDC34*		CTCTTCTACGAC-GACTACTACGAG	314.6 kb
214 ¬	07916-L07646	*ELANE*		GATCGACTCTAT-CATCCAACGCTC	64.4 kb
202 « ¬	11955-L18080	*KISS1R*		GTCCTACAGCAA-CTCCGCGCTGAA	285.3 kb
STK11 probes					
247 «	02215-L10041	Exon 1	24-25	ATGGCGGCGGCG-TGTCGGGCGCGG	0.8 kb
373 « ±	02251-L10042	Exon 1	861-862	TGAGGCCCGGGT-CCCACTGGAACT	0.3 kb
		start codon	*1137-1139 (exon 1)*		
195 «	03124-L03988	Exon 1	1204-1205	GGTGGGTATGGA-CACGTTCATCCA	11.5 kb
221 «	03125-L18081	Exon 2	1460-1461	TTACGGCACAAA-AATGTCATCCAG	0.9 kb
229 «	03126-L18082	Exon 3	1551-1552	GCATGCAGGAAA-TGCTGGACAGCG	1.1 kb
238 «	03127-L03338	Exon 4	1640-1641	GAGTACCTGCAT-AGCCAGGGCATT	0.2 kb
283 «	16639-L19597	Exon 5	1761-1762	CGGCGGACGACA-CCTGCCGGACCA	0.7 kb
292 «	03129-L03340	Exon 6	1927-1928	CTACAAGTTGTT-TGAGAACATCGG	0.7 kb
317 «	16638-L19168	Exon 7	2015-2016	CTTGAGTACGAA-CCGGCCAAGAGG	1.2 kb
337 «	03131-L02583	Exon 8	2210-2209 reverse	TAGATGATGTCA-TCCTCGATGTCG	3.4 kb
346 « ±	03132-L03990	Exon 9	2310-2311	AGGCCGTGTGTA-TGAACGGCACAG	1.1 kb
		stop codon	*2436-2438 (exon 9)*		
169 «	03891-L03986	Exon 10	2501-2502	GGCCCTCAGTCT-TCCTGCCGGTTC	

[a] See section Exon numbering on page 3 for more information.
[b] Only partial probe sequences are shown. Complete probe sequences are available at www.mrcholland.com. Please notify us of any mistakes: info@mrcholland.com.

± SNP rs372994361 strongly influences the 373 nt probe signal and has an allele frequency of more than 1:2500. SNP rs565993396 could influence the 346 nt probe signal. In case of apparent deletions, it is recommended to sequence the region targeted by this probe.
« Probe located in or near a GC-rich region. A low signal can be caused by salt contamination in the DNA sample leading to incomplete DNA denaturation, especially of GC-rich regions. The use of DNA samples containing 15 mM or more salt can result in false positive *STK11* deletion results due to incomplete denaturation.
¬ Flanking probe. Included to help determine the extent of a deletion/duplication. Copy number alterations of only the flanking or reference probes are unlikely to be related to the condition tested.

SNVs located in the target sequence of a probe can influence probe hybridization and/or probe ligation. Please note: not all known SNVs are mentioned in the tables above. Single probe aberration(s) must be confirmed by another method.

Related SALSA MLPA probemixes

- P158 JPS: Contains probes for the *BMPR1A*, *SMAD4* and *PTEN* genes.
- P225 PTEN: Contains probes for the *PTEN* gene.

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- Jiang YL et al. (2019). STK11 gene analysis reveals a significant number of splice mutations in Chinese PJS patients. *Cancer Genet*. 230:47–57.
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- Lipsa A et al. (2019). Novel germline STK11 variants and breast cancer phenotype identified in an Indian cohort of Peutz-Jeghers syndrome. *Hum Mol Genet*. 28(11):1885-1893.
- Yang HR et al. (2010). Germline mutation analysis of STK11 gene using direct sequencing and multiplex ligation-dependent probe amplification assay in Korean children with Peutz-Jeghers syndrome. *Dig Dis Sci.* 55: 3458-3465.

P101 product history	
Version	*Modification*
B4	One reference probe has been replaced and the LDLR probe has been replaced by a reference probe.
B3	One reference probe has been replaced and one flanking probe has been replaced by a reference probe.
B2	One reference probe has been replaced and one has been added.
B1	Two STK11 probes, 3 reference probes and 2 control fragments (88 and 96 nt) have been replaced. One STK11 exon 1 probe has been removed.
A2	One reference probe has been replaced and two STK11 probes have a small change in length / peak height. Extra control fragments at 100 and 105 nt have been added.
A1	First release.

Implemented changes in the product description
Version B4-08 – 27 February 2023 (04P) - Warning added to Table 1 and Table 2 for SNP that could influence probe signal of 346 nt probe 03132-L03990. - Various minor textual changes. Version B4-07 – 03 January 2022 (04P) - Precautions and warnings rewritten. - P101 specific notes updated. Version B4-06 – 21 October 2021 (04P) - Product description adapted to a new template. - Precautions and warnings updated. - P101 specific notes updated. - Warnings for probes located in or near a GC-rich region below Table 1 and Table 2 updated. - UK added to the list of European countries that accept the CE-mark. - Various minor textual changes. *Version B4-05 — 23 January 2020 (02P)* - Product description rewritten and adapted to a new template. - Intended use updated. - Ligation sites of the probes targeting the *STK11* gene updated according to new version of the NM_ reference sequence. - For uniformity, the chromosomal locations and bands in this document are now all based on hg18 (NCBI36). - An extra explanation for the DNA denaturation probes is added to the P101 specific notes section. - Selected publications using P101 STK11 updated. - Related SALSA MLPA probemixes added. *Version B4-04 – 18 December 2018 (04)* - Regulatory status section updated. - Selected publications using P101 STK11 updated.

More information: www.mrcholland.com; www.mrcholland.eu	
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RUO	ALL OTHER COUNTRIES

*comprising EU (candidate) member states and members of the European Free Trade Association (EFTA), and the UK. The product is for RUO in all other European countries.