Instructions for Use

SALSA® MLPA® Probemix P003 MLH1/MSH2

See also the MLPA General Protocol, the product descriptions of the SALSA® MLPA® Reagent Kit and SALSA® Binning DNA SD052, and the Coffalyser.Net Reference Manual.

Visit the SALSA® MLPA® Probemix P003 MLH1/MSH2 product page on our website to find Certificates of Analysis and a list of related products.

Product Name	**SALSA® MLPA® Probemix P003 MLH1/MSH2**
Version	D1
Catalogue numbers	P003-025R (25 reactions) P003-050R (50 reactions) P003-100R (100 reactions)
Basic UDI-DI	872021148P0035A
Ingredients	Synthetic oligonucleotides, oligonucleotides purified from bacteria, Tris-HCl, EDTA

Additional Test Components	**Catalogue Numbers**
SALSA® MLPA® Reagent Kit	EK1-FAM EK1-CY5 EK5-FAM EK5-CY5 EK20-FAM
SALSA® Binning DNA SD052	SD052

Storage and Shelf Life

Recommended conditions		

A shelf life of until the expiry date is guaranteed, also after opening when stored in the original packaging under recommended conditions. For the exact expiry date, see the label on the vial. This product should not be exposed to more than 25 freeze-thaw cycles. Do not use the product if the packaging is damaged or opened. Leave chemicals in original containers. Waste material must be disposed of in accordance with the national and local regulations.

Regulatory Status	
IVD	EUROPE CE 2797 COLOMBIA ISRAEL
RUO	ALL OTHER COUNTRIES

Label Symbols			
IVD	In Vitro Diagnostic	RUO	Research Use Only

More Information: www.mrcholland.com	
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Any serious incident that has occurred in relation to this product should be reported to MRC Holland and the competent authority of the Member State or country in which the user and/or the patient is located.

Changes in this Product Version

As compared to version C1, two probes specific for the recurrent 10 Mb inversion on chromosome 2p have been added and one reference probe has been replaced.

1. Intended Purpose

The SALSA MLPA Probemix P003 MLH1/MSH2 is an in vitro diagnostic (IVD)[1] or research use only (RUO) semi-quantitative manual assay[2] for the detection of deletions or duplications in the *MLH1* and *MSH2* genes and deletions of exon 9 in the *EPCAM* gene, as well as a recurrent 10 Mb inversion on chromosome arm 2p which disrupts the *MSH2* gene, in genomic DNA isolated from human peripheral whole blood specimens. P003 MLH1/MSH2 is intended to confirm a potential cause for and clinical diagnosis of Lynch syndrome, and for molecular genetic testing of at-risk family members.

Copy number variations (CNVs) detected with P003 MLH1/MSH2 should be confirmed with SALSA MLPA Probemix P248 MLH1-MSH2 Confirmation or a different technique. In particular, CNVs detected by only a single probe always require confirmation by another method. Most defects in the *MLH1* and *MSH2* genes are point mutations, none of which will be detected by MLPA. It is therefore recommended to use this assay in combination with sequence analysis. P248 MLH1-MSH2 Confirmation cannot be used to verify deletions in exon 9 of the *EPCAM* gene or the recurrent 10 Mb inversion on chromosome arm 2p.

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 IVD use in the countries specified on page 1 of this product description. In all other countries, this is a RUO product.

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

2. Sample Requirements

Specimen	50-250 ng purified human genomic DNA, dissolved in 5 µl $TE_{0.1}$ buffer, pH 8.0-8.5
Collection Method	Standard methods
Extraction Method	Methods tested by MRC Holland: • QIAGEN Autopure LS (automated) and QIAamp DNA mini/midi/maxi kit (manual) • Promega Wizard Genomic DNA Purification Kit (manual) • Salting out (manual)

Sample Types	
Test Sample	• Provided by user
Reference Samples (Required)	• Provided by user • Extraction method, tissue type, DNA concentration and treatment as similar as possible in all test and reference samples. • Have a normal copy number and ≤0.10 standard deviation for all probes except for inversion-specific probes. • At least three* independent reference samples required in each experiment for proper data normalisation. Derived from unrelated individuals from families without a history of Lynch syndrome (LS).
No-DNA Control (Preferably)	• Provided by user • $TE_{0.1}$ buffer instead of DNA • To check for DNA contamination
Binning DNA (Initial Experiment)	• SALSA Binning DNA SD052, provided by MRC Holland • Required in initial experiment to determine suitable bin set • Should never be used as a reference sample
Positive Control Samples (Preferably)	• Provided by user
Validation Samples (Required)	In the validation experiments of this probemix, the peaks of the inversion-specific probes are expected to be absent in the majority of samples from healthy individuals.

*When testing >21 samples, include one extra reference for each 7 test samples.

3. Test Procedure

See the MLPA General Protocol.

4. Quality Control, Data Analysis, and Troubleshooting

Quality Control Fragments in the Probemix	
Length (nt)	**Function**
64-70-76-82	DNA quantity control fragments
88-96	DNA denaturation control fragments
92	Benchmark fragment
100	Chromosome X presence control fragment
105	Chromosome Y presence control fragment

Coffalyser.Net should be used for data analysis in combination with the appropriate product and lot-specific Coffalyser sheet. See the Coffalyser.Net Reference Manual for details on data analysis and quality control.

For troubleshooting help, see the additional resources offered on our support portal.

5. Interpretation of Results

Determining Typical Values in Normal and Affected Populations

The typical final ratio (FR) values stated in the copy number tables were determined in a validation study with samples containing abnormal copy numbers. The standard deviation of each individual probe over all the reference samples was ≤0.10.

Expected Results of Reference Probes

Final Ratio (FR)	Copy Number	Description
0.80 – 1.20	2	Normal

Typical Results of Probes Targeting Two Copies (*MLH1*/*MSH2*/*EPCAM*)

Final Ratio (FR)	Copy Number	Description
0	0	Homozygous deletion
0.40 – 0.65	1	Heterozygous deletion
0.80 – 1.20	**2**	**Normal**
1.30 – 1.65	3	Heterozygous duplication
1.75 – 2.15	4	Homozygous duplication or Heterozygous triplication
All other values	-	Ambiguous

The tables illustrate the relationship between final probe ratio and corresponding copy number. Test results are expected to center around these values. Ambiguous values can indicate a technical problem, but may also reflect a biological cause such as mosaicism or a SNV influencing a single probe. It is important to use Coffalyser.Net to determine the significance of values found.

Possible Results of Inversion-Specific Probes

Signal Strength	Mutation Status
≥10% median peak height reference probes	10 Mb inversion with one breakpoint in MSH2 intron 7 is detected (expected only in positive samples)
<10% median peak height reference probes	10 Mb inversion with one breakpoint in *MSH2* intron 7 is not detected (expected in most samples from healthy individuals)

6. Performance Characteristics

<table>
<tr><th>Study</th><th>Description</th></tr>
<tr><td>Expected values for copy number and inversion detection in normal and affected populations</td><td>To determine the expected values in normal and affected populations a study was conducted on over 1500 MLPA reactions using samples with and without abnormal copy numbers. Cut-off values for copy number determination were verified with P003 MLH1/MSH2 in 47 samples from healthy individuals with normal copy numbers and four samples with known CNVs. The expected FRs for the corresponding copy number were found in all samples tested, with the exception of one ambiguous measurement (in a single sample from a healthy individual). The expected value for inversion-specific probes was verified using SALSA Binning DNA SD052 and the expected signal was found.</td></tr>
<tr><td>Limit of Detection</td><td>A study using representative probemixes was conducted to evaluate the minimum and maximum amount of DNA acceptable as the assay input. Results support the use of 50-250 ng of human DNA as the recommend input amount. These lower and higher limits of detection were verified using P003 MLH1/MSH2 on three samples with known CNVs/10 Mb inversion and on one sample without any mutation and expected results were obtained using both the lower and upper input amount of DNA.</td></tr>
<tr><td>Interfering substances</td><td>A study using P003 MLH1/MSH2 was performed to assess the potential for interference of endogenous and exogenous substances on genomic DNA on samples with known CNVs/10 Mb inversion status. For most probes, expected FRs (FRs within the expected cut-off category) and mutation status were obtained even in the presence of potential interferents at concentrations shown in the table below.
<table>
<tr><th>Interferent</th><th>Source</th><th>Testing Concentration</th><th>Results*</th></tr>
<tr><td>EDTA</td><td>Exogenous – specimen collection tubes</td><td>1.5 mM</td><td>Copy number: Expected FR for 573/585 measurements
Mutation: Expected signal in 30/30 measurements</td></tr>
<tr><td>NaCl</td><td>Exogenous – DNA extraction</td><td>40 mM</td><td>Copy number: Expected FR for 579/585 measurements
Mutation: Expected signal in 30/30 measurements</td></tr>
<tr><td>Fe^{3+} ($FeCl_3$)</td><td>Exogenous – DNA extraction</td><td>1 µM</td><td>Copy number: Expected FR for 584/585 measurements
Mutation: Expected signal in 30/30 measurements</td></tr>
<tr><td>Heparin</td><td>Exogenous – specimen collection tubes</td><td>0.02 U/mL</td><td>Copy number: Expected FR for 584/585 measurements
Mutation: Expected signal in 30/30 measurements</td></tr>
<tr><td>Hemoglobin</td><td>Endogenous – blood sample</td><td>0.02 µg/µl</td><td>Copy number: Expected FR for 562/585 measurements
Mutation: Expected signal in 30/30 measurements</td></tr>
</table>
* Results are summarised for all probes across all five samples tested.

Hemoglobin had the largest effect on copy number determination: final ratios within an incorrect range were obtained in almost all samples. DNA extraction methods from blood remove hemoglobin and during testing of 24 samples extracted from blood the expected final ratios were found. Therefore, it is only when hemoglobin is in excess that deviating probe signals can be found.

EDTA, NaCl, Fe^{3+}, and heparin had milder effects on copy number determination. In all deviating cases, only ambiguous measurements were obtained. Such results would at most lead to a delayed outcome, as the assay may have to be repeated. False positives or false negatives would not result from such FRs.

Importantly, warnings or errors were obtained in all affected samples using Coffalyser.Net software.

In terms of mutation status, in all cases the absence or presence of the 10 Mb inversion was correctly identified.</td></tr>
<tr><td>Cross-reactivity</td><td>Cross-reactivity is the potential for probes to bind to homologous regions (e.g. pseudogenes) or other cross-reactive sequences. Quality tests were carried out to determine whether probes are specific to their target sequence and all probes met the quality criteria for specificity.</td></tr>
<tr><td>Accuracy</td><td>Results of accuracy are derived from trueness and precision studies. For trueness, four previously genotyped samples were tested using P003 MLH1/MSH2 and found to have the expected results. Assay precision was tested by repeatedly testing samples with known copy number/10 Mb inversion over multiple days, and by multiple operators. Results showed a correct call in 2919/2925 data points for CN probes and 150/150 correct calls for inversion-specific probes, leading to a precision of >99% for CN determination and a precision of 100% for inversion status determination.</td></tr>
<tr><td>Clinical validity*</td><td>1.5-8% of LS is explained by large deletions or duplications in MLH1 (GeneReviews).

4-16% of LS is explained by large deletions or duplications in MSH2 (GeneReviews).</td></tr>
</table>

Study	Description
	1-3% of LS is explained by deletions in the last exons of *EPCAM* (Tutlewska et al. 2013). <1% of LS is explained by the 10 Mb inversion affecting chromosome arm 2p (Chen 2008, Wagner et al. 2002). *Based on a 2011-2025 literature review

Summary of Safety and Performance (SSP)
The SSP is available in the European database on medical devices (Eudamed), https://ec.europa.eu/tools/eudamed, or upon request.

Content – Probe Details Sorted by Chromosomal Position

Chr. position	Target	Exon	Distance to next probe	Mutation	Length (nt)	Probe number	Warnings
2p21	*EPCAM*	Exon 9	0.1 kb		481	18132-L24050	# ε
2p21	*EPCAM*	Exon 9	16.0 kb		472	13147-L14404	ε
2p21	*MSH2*	Upstream (Exon 1)	0.2 kb		217	13145-L14624	Ø
2p21	*MSH2*	Upstream (Exon 1)	0.7 kb		148	12036-L02162	Ø » ε
2p21	*MSH2*	Intron 1 (Exon 1)	4.8 kb		190	11287-L12006	Ø
2p21	*MSH2*	Exon 2	1.7 kb		160	00906-L00494	
2p21	*MSH2*	Exon 3	2.3 kb		172	01029-L00601	
2p21	*MSH2*	Exon 4	1.8 kb		184	00908-L00496	
2p21	*MSH2*	Exon 5	2.1 kb		211	00909-L00497	
2p21	*MSH2*	Exon 6	13.5 kb		231	15298-L17064	
2p21	*MSH2*	Exon 7	12.1 kb		249	11634-L16356	
2p21	*MSH2*	Intron 7	0.5 kb	10Mb Inversion	317	20090-SP0916-L28222	§ Ж
2p21	*MSH2*	Intron 7	3.1 kb	10Mb Inversion	265	20091-SP0917-L28216	§ Ж
2p21	*MSH2*	Exon 8	17.5 kb		269	00912-L28217	
2p21	*MSH2*	Exon 9	3.9 kb		292	00913-L28221	
2p21	*MSH2*	Intron 10 (Exon 10)	4.0 kb		310	11288-L12007	Ø
2p21	*MSH2*	Exon 11	4.1 kb		332	00915-L28223	
2p21	*MSH2*	Exon 12	1.3 kb		346	18133-L23925	
2p21	*MSH2*	Exon 13	1.9 kb		364	01013-L00575	
2p21	*MSH2*	Exon 14	2.5 kb		391	00918-L00506	
2p21	*MSH2*	Exon 15	2.0 kb		409	00919-L00585	
2p21	*MSH2*	Exon 16			427	01053-L14623	
3p22.2	*MLH1*	Exon 1	3.1 kb		142	14701-L19726	
3p22.2	*MLH1*	Exon 2	4.3 kb		154	01008-L00577	
3p22.2	*MLH1*	Exon 3	3.4 kb		166	00888-L00476	
3p22.2	*MLH1*	Exon 4	2.6 kb		178	00889-L23928	
3p22.2	*MLH1*	Exon 5	1.8 kb		203	20360-L28308	
3p22.2	*MLH1*	Exon 6	3.0 kb		224	14702-L28215	
3p22.2	*MLH1*	Exon 7	0.2 kb		242	00892-L16355	
3p22.2	*MLH1*	Exon 8	2.4 kb		256	00893-L00481	
3p22.2	*MLH1*	Exon 9	3.1 kb		278	00894-L28218	
3p22.2	*MLH1*	Exon 10	2.9 kb		301	00895-L00483	
3p22.2	*MLH1*	Exon 11	5.5 kb		326	00896-L18364	
3p22.2	*MLH1*	Exon 12	3.0 kb		340	14703-L28224	∫
3p22.2	*MLH1*	Exon 13	11.4 kb		355	00898-L23926	
3p22.2	*MLH1*	Exon 14	2.1 kb		382	00899-L00586	
3p22.2	*MLH1*	Exon 15	5.3 kb		401	00900-L00488	
3p22.2	*MLH1*	Exon 16	1.0 kb		418	01009-L00576	
3p22.2	*MLH1*	Exon 17	0.4 kb		436	01030-L00602	
3p22.2	*MLH1*	Exon 18	1.8 kb		445	01031-L00603	
3p22.2	*MLH1*	Exon 19			454	12094-L12994	
1p	Reference				287	18920-L25191	
2q	Reference				236	15941-L18067	
4q	Reference				375	00681-L11147	
5q	Reference				130	00797-L21056	
7q	Reference				196	17056-L20134	
10p	Reference				463	00979-L00568	
10p	Reference				136	00981-L00566	
13q	Reference				490	04274-L24051	
14q	Reference				499	14882-L21050	±

Probe lengths may vary slightly depending on capillary electrophoresis instrument settings. Please see the most up to date Coffalyser sheet for exact probe lengths obtained at MRC Holland.
The *EPCAM, MSH2,* and *MLH1* exon numbers are derived from MANE project and are based on MANE Select transcript. For more information, see the probe sequences document available on the product page at www.mrcholland.com. Annotations of several probes with targets at the edge of or slightly outside the coding region, were altered. The exon numbering for *MSH2* of product description version D1-09 is disclosed between brackets.
Chromosomal bands are based on: hg18.

7. Precautions and Warnings

Probe warnings

§	These probes will only generate a signal when the inversion is present.
±	The presence of single nucleotide variant (SNV) rs147586703 can affect the signal of this probe.
Ж	These probes consist of three parts and have two ligation sites. A low signal of these probes can be due to depurination of the sample DNA, e.g. due to insufficient buffering capacity or a prolonged denaturation time.
Ø	These probes target sequences outside of the known coding region. Copy number alterations of only one of these probes are of unknown clinical significance.
#	The specificity of this probe relies on a single nucleotide difference compared to a related gene or pseudogene. As a result, an apparent duplication of only this probe can be the result of a non-significant single nucleotide sequence change in the related gene or pseudogene.
»	This probe detects the same sequence as the 355 nt probe in SALSA® MLPA® Probemix P248 MLH1-MSH2 Confirmation.
ε	The 481 nt, 472 nt, and 148 nt probes detect the same sequences as the 470 nt, 429 nt, and 358 nt probes, respectively in SALSA® MLPA® Probemix P072 MSH6-MUTYH.
∫	This probe has been found to give false positive deletion/duplication results. This is probably due to an unusual low sensitivity of this probe to sample DNA depurination. Reduced signals of other probes caused by sample depurination lead to seemingly high signals of this probe. Depurination of sample DNA can occur in samples with insufficient buffering capacity. The 400 nt probe in the P248 probemix does not have this problem and can be used for confirmation. More information on sample DNA depurination is available on www.mrcholland.com.

Probemix-specific precautions

1. This product is not known to contain any harmful agents. Based on the concentrations present, none of the ingredients are hazardous as defined by the Hazard Communication Standard. **A Safety Data Sheet (SDS) is not required for this product**: none of the ingredients contain dangerous substances at concentrations requiring distribution of an SDS (as per Regulation (EC) No 1272/2008 [EU-GHS/CLP] and 1907/2006 [REACH] and amendments).
2. Sample or technical artefacts may appear as a (mosaic) copy number change of the whole/partial gene. Whole/partial gene deletions or duplications should therefore be confirmed by analysis of an independent DNA sample, to exclude false positive results.
3. Small changes (e.g. SNVs, small indels) in the sequence targeted by a probe can cause false positive results, even when >20 nt from the probe ligation site. Sequence changes 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. Deviations detected by this product should be confirmed, and single-probe deviations always require confirmation. Sequencing of the target region is recommended. Please contact MRC Holland for more information: info@mrcholland.com.
4. SNV rs147586703 mentioned in this document requires additional caution. Please note that any probe can be affected by known or novel SNVs.
5. Copy number alterations of reference probes are unlikely to be related to the condition tested.
6. Before testing patient samples, testing of samples from healthy individuals is required to identify suitable reference samples for proper data analysis.
7. Lynch syndrome due to *MLH1*, *MSH2*, or *EPCAM* gene defects is an autosomal dominant disorder. A heterozygous deletion of one or more *MLH1* or *MSH2* exons that are present in the major transcript variants, NM_000249.4 (MLH1) and NM_000251.3 (MSH2), is expected to result in Lynch syndrome.
8. Simultaneous deletion of the 472 nt and 481 nt EPCAM probes is a strong indication that the last *EPCAM* exon (exon 9) is disrupted, which can lead to methylation of the adjacent *MSH2* promoter and inactivation of *MSH2* (Kovacs et al. 2009, Ligtenberg et al. 2009).
9. The presence of a peak at 265 nt and/or 317 nt is an indication that the 10 Mb chromosome 2 inversion is present in the sample DNA (Chen 2008, Rhees et al. 2014, Wagner et al. 2002). These probes do not generate a signal on normal samples. Please note that the peak height of these two probes can be strongly affected by DNA fragmentation. The 20091-SP0917-L28216 probe present at 265 nt and the 20090- SP0916-L28222 probe present at 317 nt require an intact DNA fragment to bind to of at least 220 nt or 520 nt, respectively, in inversion positive DNA samples, which is much longer than the length requirements for other MLPA probes (60-80 nt). DNA samples in which both probes show a clear peak, as well as samples in which a clear peak for only one of the two probes is observed, should be further investigated even when these peaks are much lower than obtained on the SD052 Binning DNA sample. A non-specific peak close to the 265 nt peak can appear if the ligation reaction is performed at a temperature below 54°C.
10. A duplication of an internal part of a gene usually results in a defective copy of that gene, as the duplicated sequence is typically located directly adjacent to the original sequence, resulting in a defective transcript. However, duplication of the complete *MLH1* or *MSH2* gene is not expected to result in disease. Please note that 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.
11. The presence of a processed *MLH1* pseudogene is a rare finding and may result in the apparent duplication of multiple MLH1 probes. Such processed pseudogenes lack introns and potentially several exons, leading to an irregular pattern of duplication and discrepant copy number results between P003 MLH1/MSH2 and P248 MLH1-MSH2 Confirmation.

Technique-specific precautions
See the MLPA General Protocol.

8. Limitations

Probemix-specific limitations

1. The inversion-specific probes can only detect the presence of the inversion and should not be used to determine zygosity.
2. SALSA MLPA P003 MLH1/MSH2 should not be used to confirm results of SALSA MLPA Probemix P072 MSH6-MUTYH, and vice versa, as some probes share the same ligation site (see probe warning ε). In case CNVs are found in the *MSH2* and/or *EPCAM* gene, a different method should be used to confirm the results.

Technique-specific limitations
See the MLPA General Protocol.

9. References Cited in this IFU

1. Chen JM (2008). The 10-Mb paracentric inversion of chromosome arm 2p in activating MSH2 and causing hereditary nonpolyposis colorectal cancer: re-annotation and mutational mechanisms. Genes Chromosomes Cancer. 47:543-545.
2. Kovacs ME et al. (2009). Deletions removing the last exon of TACSTD1 constitute a distinct class of mutations predisposing to Lynch syndrome. Hum Mutat. 30:197-203.
3. Ligtenberg MJ et al. (2009). Heritable somatic methylation and inactivation of MSH2 in families with Lynch syndrome due to deletion of the 3' exons of TACSTD1. Nat Genet. 41:112-117.
4. Rhees J et al. (2014). Inversion of exons 1-7 of the MSH2 gene is a frequent cause of unexplained Lynch syndrome in one local population. Fam Cancer. 13:219-225.
5. Tutlewska K et al. (2013). Germline deletions in the EPCAM gene as a cause of Lynch syndrome - literature review. Hered Cancer Clin Pract. 11:9.
6. Wagner A et al. (2002). A 10-Mb paracentric inversion of chromosome arm 2p inactivates MSH2 and is responsible for hereditary nonpolyposis colorectal cancer in a North-American kindred. Genes Chromosomes Cancer. 35:49-57.

Implemented changes in the product description

Version D1-11 – 10 August 2026 (03S)
- In section 2. Sample Requirements, statement requiring specimens to be free from heparin was removed.
- Several textual changes were made in section 6. Performance Characteristics (no changes to probemix-specific results).
- The Ø warning was removed for the inversion-specific probes in the probe content table.
- The Ж warning was updated in section 7. Precautions and Warnings.
- A precaution was added for the presence of processed *MLH1* pseudogenes in section 7. Precautions and Warnings.

Version D1-10 – 17 September 2025 (03S)
- Product description adapted to a new template.
- Intended purpose updated, specifying assay is manual, that only deletions in exon 9 of *EPCAM* can be detected, and that P248 MLH1-MSH2 Confirmation cannot be used to verify deletions in exon 9 of the *EPCAM* gene or the recurrent 10 Mb inversion on chromosome arm 2p.
- Description of probe targets at the edge of or slightly outside the coding region has been adjusted. No change in actual target sites.
- SNVs rs1800146, rs55907433, and rs146577635 can affect the probe signal. However, the warnings for these SNVs present in previous product description versions have been replaced by a general warning for small sequence changes, included in section Precautions and Warnings.
- Warning for target sequences outside of the known coding region added for probes 13145-L14624, 12036-L02162, 11287-L12006, 20090-SP0916-L28222, 20091-SP0917-L28216, and 11288-L12007.
- Warning for probes targeting the same sequence as those present in P072 MSH6-MUTYH added for probes 18132-L24050, 13147-L14404, and 12036-L02162.
- Limitation regarding the use of P072 MSH6-MUTYH as a confirmation mix was added.
- Probemix is now IVDR certified.