Instructions for Use

SALSA® MLPA® Probemix P065 Marfan Syndrome-1 & SALSA® MLPA® Probemix P066 Marfan Syndrome-2

See also the MLPA General Protocol, the product description of the SALSA® MLPA® Reagent Kit, and the Coffalyser.Net Reference Manual.

Visit the SALSA® MLPA® Probemix P065 Marfan Syndrome-1 and the SALSA® MLPA® Probemix P066 Marfan Syndrome-2 product pages on our website to find Certificates of Analysis and a list of related products.

Product Name	**SALSA® MLPA® Probemixes P065 Marfan Syndrome-1**
Version	C1
Catalogue numbers	P065-025R (25 reactions) P065-050R (50 reactions) P065-100R (100 reactions)
Basic UDI-DI	872021148P0655Y
Ingredients	Synthetic oligonucleotides, oligonucleotides purified from bacteria, Tris-HCl, EDTA

Product Name	**SALSA® MLPA® Probemix P066 Marfan Syndrome-2**
Version	C1
Catalogue numbers	P066-025R (25 reactions) P066-050R (50 reactions) P066-100R (100 reactions)
Basic UDI-DI	872021148P06662
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

Storage and Shelf Life

Recommended conditions	-25°C -15°C	☀

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 ISRAEL
RUO	ALL OTHER COUNTRIES

Label Symbols			
IVD	In Vitro Diagnostic	RUO	Research Use Only

More Information: **www.mrcholland.com**	
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E-mail	info@mrcholland.com (information & technical questions); order@mrcholland.com (orders)
Phone	+31 888 657 200

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 of P065

As compared to version B1, one FBN1 target probe and three reference probes have been replaced. Several probes have been modified in length but not in the sequence detected.

Changes in this Product Version of P066

As compared to version B2, two FBN1 target probes have been replaced and one FBN1 promoter probe has been added. Also, five reference probes have been replaced.

1. Intended Purpose

The SALSA MLPA Probemix P065 Marfan Syndrome-1 and SALSA MLPA Probemix P066 Marfan Syndrome-2 are in vitro diagnostic (IVD)[1] or research-use only (RUO) semi-quantitative manual assays[2] for the detection of deletions or duplications in the *FBN1* gene, in order to confirm a potential cause for and clinical diagnosis of Marfan syndrome and other *FBN1*-related disorders. Both assays are for use with genomic DNA isolated from human peripheral whole blood specimens and are also intended for molecular genetic testing of at-risk family members[3].

The detection of copy number variations (CNVs) in *FBN1* requires the use of both SALSA MLPA Probemix P065 Marfan Syndrome-1 and SALSA MLPA Probemix P066 Marfan Syndrome-2. CNVs detected with SALSA MLPA Probemix P065 Marfan Syndrome-1 and SALSA MLPA Probemix P066 Marfan Syndrome-2 should be confirmed with a different technique. In particular, CNVs detected by only a single probe always require confirmation by another method. Most defects in the *FBN1* 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.

These devices are 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.

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. • At least three* independent reference samples required in each experiment for proper data normalisation. Derived from unrelated individuals from families without a history of Marfan syndrome.	
No-DNA Control (Preferably)	• Provided by user • TE$_{0.1}$ buffer instead of DNA • To check for DNA contamination	
Positive Control Samples (Preferably)	• Provided by user, or	
	Available from third parties	See the table of positive samples on the probemix product page on our website.

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

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[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.

[3] Certain probes targeting additional genes included in P065 Marfan Syndrome-1 may only be used in a research setting. The following table summarises which probes are for IVD use or exclusively restricted to be used in a research setting:

	IVD Targets	RUO Targets
P065	*FBN1*	*TGFBR2*
P066	*FBN1*	*N.A.*

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(*FBN1/TGFBR2*)

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 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.

6. Performance Characteristics

Study	Description
Expected values for copy number in normal and affected populations	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. When the standard deviation of each individual probe over all the reference samples is ≤0.10, the ranges stated in the copy number table above can be used. Cut-off values for copy number determination were verified with SALSA MLPA Probemix P065 Marfan Syndrome-1 and SALSA MLPA Probemix P066 Marfan Syndrome-2 in 45 and 44 samples from healthy individuals with normal copy number, respectively, and three samples with known CNVs. The expected final ratios for the corresponding copy number were found in all samples tested.
Limit of detection	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. The use of insufficient or too much sample DNA can affect performance. These lower and higher limits of detection were verified using SALSA MLPA Probemix P065 Marfan Syndrome-1 and SALSA MLPA Probemix P066 Marfan Syndrome-2 in three samples with known CNVs and a sample with normal copy number, and expected results were obtained using both the lower and upper input amount of DNA.
Interfering substances	SNVs or other polymorphisms (e.g. indels) in the DNA target sequence and impurities in the DNA sample (e.g. NaCl or KCl, EDTA and hemoglobin) can affect the MLPA reaction. A study using SALSA MLPA Probemix P065 Marfan Syndrome-1 and SALSA MLPA Probemix P066 Marfan Syndrome-2 was performed to assess the potential for interference of endogenous and exogenous substances on genomic DNA on samples with known copy number status and one wildtype sample, see table below.

Interferent	Source	Testing Concentration	Results*
EDTA	Exogenous – specimen collection tubes	1.5 mM	P065: Expected FR for 395/408 measurements P066: Expected FR for 391/420 measurements
NaCl	Exogenous – DNA extraction	40 mM	P065: Expected FR for 399/408 measurements P066: Expected FR for 419/420 measurements
Fe^{3+} ($FeCl_3$)	Exogenous – DNA extraction	1 µM	P065: Expected FR for 388/408 measurements P066: Expected FR for 420/420 measurements
Heparin	Exogenous – specimen collection tubes	0.02 U/mL	P065: Expected FR for 406/408 measurements P066: Expected FR for 420/420 measurements

<table>
<tr><th>Study</th><th>Description</th></tr>
<tr><td></td><td>
<table>
<tr><td>Hemoglobin</td><td>Endogenous – blood sample</td><td>0.02 µg/µl</td><td>P065: Expected FR for 330/408 measurements
P066: Expected FR for 260/420 measurements</td></tr>
</table>
* Results are summarised for all FBN1 probes (P065: 34, P066: 36) across four samples tested in triplicate.

For both P065 and P066, hemoglobin had the largest effect on copy number determination: final ratios within an incorrect range were obtained in all samples. Importantly, warnings or errors were obtained in all affected samples using Coffalyser.Net software. DNA extraction methods from blood remove hemoglobin and during testing of 22 and 21 samples extracted from blood, respectively, the expected final ratios were found. Therefore, it is only when hemoglobin is in excess that deviating probe signals can be found. The presence of EDTA, NaCl, and for P065 also $FeCl_3$, led to false results being obtained for several measurements. In these cases, the Coffalyser.Net software also issued warnings in all affected samples.

To minimise variability across samples, 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.
</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, three previously genotyped samples were tested using SALSA MLPA Probemix P065 Marfan Syndrome-1 and SALSA MLPA Probemix P066 Marfan Syndrome-2 and found to have the expected results. Assay precision was tested by repeatedly testing samples with known copy number over multiple days, and by multiple operators. Results showed a correct call in 2436/2448 and 2081/2100 data points, respectively, leading to a precision of 99% for SALSA MLPA Probemix P065 Marfan Syndrome-1 and 99% for SALSA MLPA Probemix P066 Marfan Syndrome-2.</td></tr>
<tr><td>Clinical validity*</td><td><i>FBN1</i>: deletions and duplications in the <i>FBN1</i> gene are found in ~5% of Marfan syndrome patients (Baetens et al. 2011; Hilhorst-Hofstee et al. 2011; Mannucci et al. 2020; Rand-Hendriksen et al. 2007; Stengl et al. 2020).

*(Based on a 2006-2024 literature review)</td></tr>
</table>

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 P065 – Probe Details Sorted by Chromosomal Position

Chr. position	Target	Exon	Distance to next probe	Length (nt)	Probe number	Warnings
3p24.1	*TGFBR2*	Exon 1	0.2 kb	382	02795-L29999	
3p24.1	*TGFBR2*	Exon 1	16.4 kb	408	04665-L29657	
3p24.1	*TGFBR2*	Intron 1 (Exon 2)	21.6 kb	493	17196-L20421	Ø
3p24.1	*TGFBR2*	Exon 2 (3)	5.5 kb	196	03861-L03610	
3p24.1	*TGFBR2*	Exon 3 (4)	21.4 kb	208	17167-L21489	
3p24.1	*TGFBR2*	Exon 4 (5)	2.5 kb	256	03863-L03246	
3p24.1	*TGFBR2*	Exon 5 (6)	14.3 kb	292	03864-L03247	
3p24.1	*TGFBR2*	Exon 6 (7)	3.0 kb	328	03865-L03248	
3p24.1	*TGFBR2*	Exon 7 (8)		172	02797-L20835	
15q21.1	*FBN1*	Exon 64	5.2 kb	305	21276-L29920	
15q21.1	*FBN1*	Exon 63	0.9 kb	400	17169-L20794	
15q21.1	*FBN1*	Exon 62	3.7 kb	136	17174-L20399	+
15q21.1	*FBN1*	Exon 60	3.0 kb	471	17193-L20795	
15q21.1	*FBN1*	Exon 57	6.2 kb	346	04337-L20895	
15q21.1	*FBN1*	Exon 54	2.8 kb	314	21277-L29639	
15q21.1	*FBN1*	Exon 52	0.4 kb	178	17175-L20790	
15q21.1	*FBN1*	Exon 51	6.8 kb	268	03933-L21562	
15q21.1	*FBN1*	Exon 49	0.8 kb	363	17191-L20416	
15q21.1	*FBN1*	Exon 48	1.4 kb	232	03932-L21132	
15q21.1	*FBN1*	Exon 47	13.5 kb	154	03931-L03386	
15q21.1	*FBN1*	Exon 43	3.7 kb	184	03930-L03385	
15q21.1	*FBN1*	Exon 41	4.0 kb	427	03929-L03750	
15q21.1	*FBN1*	Exon 38	0.5 kb	263	17184-L20409	
15q21.1	*FBN1*	Exon 37	4.1 kb	391	03928-L03383	
15q21.1	*FBN1*	Exon 35	9.1 kb	337	03927-L03382	
15q21.1	*FBN1*	Exon 32	2.2 kb	287	03926-L20793	
15q21.1	*FBN1*	Exon 31	3.5 kb	238	03925-L03380	
15q21.1	*FBN1*	Exon 28	0.8 kb	244	17182-L20407	
15q21.1	*FBN1*	Exon 27	0.1 kb	226	03924-L21131	
15q21.1	*FBN1*	Exon 26	1.6 kb	281	17186-L20411	+
15q21.1	*FBN1*	Exon 25	5.3 kb	160	03922-L20371	
15q21.1	*FBN1*	Exon 22	0.4 kb	463	03921-L20374	
15q21.1	*FBN1*	Exon 21	0.6 kb	299	21260-L29919	
15q21.1	*FBN1*	Exon 20	1.2 kb	418	03920-L03375	
15q21.1	*FBN1*	Exon 19	7.7 kb	373	03919-L03374	
15q21.1	*FBN1*	Exon 16	3.5 kb	319	03918-L03373	
15q21.1	*FBN1*	Exon 15	5.0 kb	274	03917-L21563	
15q21.1	*FBN1*	Exon 13	2.7 kb	214	17168-L29998	
15q21.1	*FBN1*	Exon 11	21.3 kb	480	17195-L21507	
15q21.1	*FBN1*	Exon 7	73.1 kb	190	03915-L03370	
15q21.1	*FBN1*	Exon 4	33.9 kb	167	03914-L20834	
15q21.1	*FBN1*	Exon 2	1.0 kb	142	04513-L14408	
15q21.1	*FBN1*	Exon 1		220	17179-L20404	
1p	Reference			250	18915-L24510	
2p	Reference			504	09870-L19465	
2q	Reference			436	12790-L13925	
4q	Reference			445	09107-L09166	
5q	Reference			130	00797-L19287	
7p	Reference			202	15424-L17583	
7q	Reference			454	19329-L25556	
8q	Reference			149	10056-L10480	
18q	Reference			355	10134-L10596	

Content P066 – Probe Details Sorted by Chromosomal Position

Chr. position	Target	Exon	Distance to next probe	Length (nt)	Probe number	Warnings
15q21.1	*FBN1*	Exon 66	0.8 kb	364	19502-L26792	
15q21.1	*FBN1*	Exon 66	1.2 kb	436	02477-L01921	
15q21.1	*FBN1*	Exon 65	0.1 kb	409	02476-L01920	
15q21.1	*FBN1*	Exon 65	9.3 kb	208	17178-L20403	Δ
15q21.1	*FBN1*	Exon 61	3.8 kb	232	02775-L26889	
15q21.1	*FBN1*	Exon 59	2.0 kb	244	17181-L20406	
15q21.1	*FBN1*	Exon 58	2.9 kb	346	02473-L01917	
15q21.1	*FBN1*	Exon 56	2.2 kb	463	17192-L20417	
15q21.1	*FBN1*	Exon 55	4.1 kb	202	17177-L20402	
15q21.1	*FBN1*	Exon 53	4.8 kb	481	17194-L21455	
15q21.1	*FBN1*	Exon 50	7.1 kb	256	02469-L01913	
15q21.1	*FBN1*	Exon 46	3.8 kb	391	02774-L01912	
15q21.1	*FBN1*	Exon 45	4.2 kb	214	02467-L20809	
15q21.1	*FBN1*	Exon 44	6.4 kb	190	17176-L20401	
15q21.1	*FBN1*	Exon 42	2.4 kb	178	02465-L01909	
15q21.1	*FBN1*	Exon 40	0.3 kb	282	21259-L29867	
15q21.1	*FBN1*	Exon 39	4.8 kb	160	02464-L01908	
15q21.1	*FBN1*	Exon 36	3.7 kb	148	21281-L29661	
15q21.1	*FBN1*	Exon 34	0.3 kb	292	02773-L21454	
15q21.1	*FBN1*	Exon 33	10.9 kb	319	17528-L20415	
15q21.1	*FBN1*	Exon 30	1.7 kb	427	02461-L20803	
15q21.1	*FBN1*	Exon 29	5.4 kb	400	02460-L01904	
15q21.1	*FBN1*	Exon 24	1.7 kb	382	02459-L01903	
15q21.1	*FBN1*	Exon 23	4.8 kb	226	17180-L21453	
15q21.1	*FBN1*	Exon 18	4.8 kb	445	02772-L20802	
15q21.1	*FBN1*	Exon 17	6.3 kb	337	02457-L01901	
15q21.1	*FBN1*	Exon 14	5.3 kb	310	02456-L01900	
15q21.1	*FBN1*	Exon 12	5.3 kb	263	17183-L20408	
15q21.1	*FBN1*	Exon 10	5.5 kb	269	02454-L20806	
15q21.1	*FBN1*	Exon 9	7.9 kb	250	02453-L20807	
15q21.1	*FBN1*	Exon 8	62.3 kb	220	02452-L01896	
15q21.1	*FBN1*	Exon 6	3.8 kb	184	02450-L01894	
15q21.1	*FBN1*	Exon 5	12.9 kb	172	02449-L01893	
15q21.1	*FBN1*	Exon 3	31.7 kb	166	21278-L30097	
15q21.1	*FBN1*	Exon 2	2.0 kb	142	02447-L01891	
15q21.1	*FBN1*	Upstream		299	21282-L29868	Ø
1p	Reference			373	13280-L14613	
1q	Reference			136	20515-L28105	
2q	Reference			355	10293-L10805	
5q	Reference			130	00797-L19287	
6p	Reference			154	10694-L11276	
7q	Reference			454	15515-L17370	
8q	Reference			238	10089-L10513	
9q	Reference			418	19751-L26534	
11p	Reference			490	14431-L21456	
13q	Reference			196	19221-L25907	
17q	Reference			472	18688-L14387	
19p	Reference			328	21112-L29527	
22q	Reference			286	12438-L13439	

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 *FBN1* and *TGFBR2* 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. The exon numbering from the previous version of this product description is disclosed between brackets.
Chromosomal bands are based on: hg18.

7. Precautions and Warnings

Probe warnings

Δ This probe may be sensitive to certain experimental variations. Aberrant results should be treated with caution.

\+ The ligation site of this probe is >20 nt away from the nearest exon in the MANE select transcript. For more information, download the probe sequences document available on the product page at www.mrcholland.com.

Ø This probe targets a sequence outside of the known coding region. Copy number alterations of only this probe are of unknown clinical significance.

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. Copy number alterations of reference probes are unlikely to be related to the condition tested.
5. Mosaicism has been reported in individuals with Marfan syndrome. Mosaic *FBN1* cases identified with the P065 Marfan Syndrome-1 and P066 Marfan Syndrome-2 probemixes must be confirmed by analysis of a second, independently collected DNA sample or a different technique.

Technique-specific precautions
See the MLPA General Protocol.

8. Limitations

Probemix-specific limitations
1. Target probes for *TGFBR2* are included for research purposes only and not for diagnostic use.

Technique-specific limitations
See the MLPA General Protocol.

9. References Cited in this IFU

1. Baetens M et al. (2011). Applying massive parallel sequencing to molecular diagnosis of Marfan and Loeys-Dietz syndromes. *Hum Mutat.* 32:1053-1062.
2. Hilhorst-Hofstee Y et al. (2011). The clinical spectrum of complete FBN1 allele deletions. *Eur J Hum Genet.* 19:247-252.
3. Mannucci L et al. (2020). Mutation analysis of the FBN1 gene in a cohort of patients with Marfan Syndrome: A 10-year single center experience. *Clin Chim Acta.* 501:154-164.
4. Rand-Hendriksen S et al. (2007). Search for correlations between FBN1 genotype and complete Ghent phenotype in 44 unrelated Norwegian patients with Marfan syndrome. *Am J Med Genet A.* 143A:1968-1977.
5. Stengl R et al. (2020). Optimising the mutation screening strategy in Marfan syndrome and identifying genotypes with more severe aortic involvement. *Orphanet J Rare Dis.* 15:290.

Implemented changes in the product description
Version C1/C1-05 – 28 March 2025 (03S) - Product description updated to a new template. - Intended purpose modified by removal of the *TGFBR2* gene and *TGFBR2*-related disorders. - Specification regarding the use of TGFBR2 probes added to section Limitations. - Exon numbering updated for seven out of nine TGFBR2 probes. - Warning for a ligation site >20nt away from the nearest exon added to probes 17174-L20399 and 17186-L20411. - Warning for target outside the transcript region added for probes 17196-L20421 and 21282-L29868. - SNVs rs138010137, rs184395862, and rs201273354 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. - Performance characteristics updated with data from analytical performance experiments. - Probemix is now IVDR-certified.