Product Description
SALSA® MLPA® Probemix P347-A3 Hemochromatosis

To be used with the MLPA General Protocol.

Version A3
For complete product history see page 8.

Catalogue numbers:
- **P347-025R:** SALSA MLPA Probemix P347 Hemochromatosis, 25 reactions.
- **P347-050R:** SALSA MLPA Probemix P347 Hemochromatosis, 50 reactions.
- **P347-100R:** SALSA MLPA Probemix P347 Hemochromatosis, 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.

General information
The SALSA MLPA Probemix P347 Hemochromatosis is a **research use only (RUO)** assay for the detection of deletions or duplications in the *HFE*, *TFR2*, *HFE2 (HJV)*, *HAMP*, and *SLC40A1* genes, which are associated with hereditary hemochromatosis (HH). This probemix can also be used to detect the presence of the *HFE* C282Y point mutation (c.845G>A/p.Cys282Tyr) and it detects the wildtype allele of the *HAMP* G71D point mutation (c.212G>A/p.Gly71Asp).

HH is an inherited disorder characterised by progressive iron deposition and tissue injury in multiple organs. HH has been demonstrated to result from mutations in several genes involved in the regulation of iron homeostasis such as *HFE*, *TFR2*, *HFE2*, *HAMP* and *SLC40A1*. Mutations in these genes act in an autosomal recessive manner, except for *SLC40A1* which manifests in autosomal dominant phenotypes. The most common form of HH is associated with the homozygous C282Y mutation of the *HFE* gene which accounts for 83% of the cases (Alexander et al. 2009).

More information is available at https://www.ncbi.nlm.nih.gov/books/NBK1440/, https://www.ncbi.nlm.nih.gov/books/NBK1349/, and https://www.ncbi.nlm.nih.gov/books/NBK1170/.

This SALSA MLPA probemix is not CE/FDA registered for use in diagnostic procedures. Purchase of this product includes a limited license for research purposes.

Gene structure and transcript variants:
Entrez Gene shows transcript variants of each gene: http://www.ncbi.nlm.nih.gov/sites/entrez?db=gene
For NM_ mRNA reference sequences: http://www.ncbi.nlm.nih.gov/sites/entrez?db=nucleotide
Locus Reference Genomic (LRG) database: http://www.lrg-sequence.org/

Exon numbering
The *HFE2* (*HJV*), *SLC40A1*, *HFE*, *TFR2* and *HAMP* exon numbering used in this P347-A3 Hemochromatosis product description is the exon numbering from the NG_011568.1, LRG_837, LRG_748, NG_007989.1 and LRG_791 sequences respectively. 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 or NG

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 P347-A3 Hemochromatosis contains 44 MLPA probes with amplification products between 136 and 481 nucleotides (nt). This includes three probes for the *HFE2* (*HJV*) gene, eight probes for the *SLC40A1* gene (one for each exon), ten probes for the *HFE* gene (one for each exon), eight probes for the *TFR2* gene and three probes for the *HAMP* gene (one for each exon). Furthermore, this probemix contains one probe specific for the *HFE* C282Y point mutation, which will only generate a signal when the mutation is present. It also contains one probe specific for the G71D point mutation within the *HAMP* gene, which will only generate a signal when the wild-type allele is present. A reduced signal can point towards the presence of the mutation **or** a deletion of exon 3. In addition, ten 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, 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 hereditary hemochromatosis. 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. Sample ID numbers NA03918 and NA11213 from the Coriell Institute have been tested with this P347-A3 probemix at MRC Holland and can be used as positive control samples to detect a heterozygous deletion of the *SLC40A1* gene. The quality of cell lines can change; therefore samples should be validated before use.

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 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 a decreased probe signal, in particular for probes located in or near a 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.

Limitations of the procedure

- In most populations, the major cause of genetic defects in the *HFE2, SLC40A1*, *HFE, TFR2*, and *HAMP* gene are small (point) mutations, none of which, except for the *HFE* C282Y and *HAMP* G71D mutations, will be detected by using SALSA MLPA Probemix P347 Hemochromatosis.
- 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.

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.

***HFE2*, *SLC40A1*, *HFE*, *TFR2* and *HAMP* mutation databases**

https://databases.lovd.nl/shared/genes/HFE2
https://databases.lovd.nl/shared/genes/SLC40A1
https://databases.lovd.nl/shared/genes/HFE
https://databases.lovd.nl/shared/genes/TFR2
https://databases.lovd.nl/shared/genes/HAMP

We strongly encourage users to deposit positive results in the Leiden Open Variation 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 *SLC40A1* exons 5 and 7 but not exon 6) to MRC Holland: info@mrcholland.com.

Table 1. SALSA MLPA Probemix P347-A3 Hemochromatosis

Length (nt)	SALSA MLPA probe	Chromosomal position (hg18)[a]					
		Reference	*HFE2*	*SLC40A1*	*HFE*	*TFR2*	*HAMP*
64-105	Control fragments – see table in probemix content section for more information						
136	Reference probe 11367-L12092	17q					
143	**SLC40A1 probe** 14324-L15993			**Exon 7**			
148	**HFE2 probe** 14325-L16812		**Exon 3**				
154	**SLC40A1 probe** 14326-L15995			**Exon 3**			
160	**HFE probe** 14327-L15996				**Exon 3**		
166	Reference probe 10904-L11573	9q					
172 Ж	**SLC40A1 probe** 14328-SP0151-L15997			**Exon 5**			
178	**HFE probe** 14329-L15998				**Exon 3**		
184	**SLC40A1 probe** 14330-L15999			**Exon 6**			
190	**TFR2 probe** 14331-L16000					**Exon 1**	
202	Reference probe 05292-L21125	3q					
208 Ж	**HFE probe** 14333-SP0152-L16813				**Exon 1**		
215	**SLC40A1 probe** 14334-L16003			**Exon 2**			
221	**HFE probe** 14335-L16004				**Exon 5**		
226	**TFR2 probe** 14336-L16407					**Exon 15**	
233 Ж	**SLC40A1 probe** 14337-SP0153-L16006			**Exon 8**			
238 *	Reference probe 20204-L27492	5q					
244	**HFE probe** 14338-L16007				**Exon 2**		
250 Ж	**HAMP probe** 14339-SP0154-L16408						**Exon 2**
256	**HFE2 probe** 14340-L16009		**Exon 1**				
265	**TFR2 probe** 14341-L16010					**Exon 4**	
274 Ж	**HFE probe** 14342-SP0155-L16011				**Exon 6**		
283	Reference probe 13346-L14772	18q					
292 ∞	**HAMP probe** 14343-L16012						**G71D wild type**
301	**HFE probe** 14344-L16013				**Exon 2**		
311	**TFR2 probe** 14727-L24427					**Exon 10**	
320	**SLC40A1 probe** 14346-L16015			**Exon 4**			
328	**TFR2 probe** 14347-L16016					**Exon 7**	
337 *	Reference probe 17370-L21036	20q					
346	**HFE probe** 14348-L16017				**Exon 5**		
355 Ж	**HAMP probe** 14349-SP0156-L16018						**Exon 1**
364 Ж	**HFE probe** 14350-SP0157-L16019				**Exon 6**		
373	**TFR2 probe** 14351-L16020					**Exon 18**	
382	**HFE2 probe** 14352-L16021		**Exon 2**				
391 *	Reference probe 18069-L22459	16q					
400	Reference probe 10091-L10515	8q					
409 § Ж	**HFE probe** 14354-SP0158-L16030				**C282Y mutation**		
419	**HFE probe** 14355-L16024				**Exon 4**		
427	**SLC40A1 probe** 14356-L16633			**Exon 1**			
436 Ж	**HAMP probe** 14729-SP0159-L16028						**Exon 1**
445	Reference probe 12758-L13874	4q					
453	**TFR2 probe** 14728-L16026					**Exon 3**	
472	**TFR2 probe** 14360-L16029					**Exon 14**	
481 «	Reference probe 13861-L15380	10q					

[a] See section Exon numbering on page 1 for more information.

* New in version A3.

§ Mutation-specific probe. This probe will only generate a signal when the C282Y mutation is present. It has been tested on artificial DNA **but not on positive human samples!**

∞ Wild type sequence detected. A lowered probe signal can be due to the G71D mutation. Other variants near the ligation site can also cause a lowered signal. A positive result must be confirmed by another method.

« 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.

Ж This probe consists of three parts and has two ligation sites. A low signal of this probe can be due to depurination of the sample DNA, e.g. due to insufficient buffering capacity or a prolonged denaturation time. When this occurs in reference samples, it can look like an increased signal in the test samples.

SNVs located in the target sequence of a probe can influence probe hybridization and/or probe ligation. Single probe aberration(s) must be confirmed by another method.

Table 2. P347-A3 probes arranged according to chromosomal location

Table 2a. *HFE2* gene

Length (nt)	SALSA MLPA probe	*HFE2* exon[a]	Ligation site NM_213653.4	Partial sequence[b] (24 nt adjacent to ligation site)	Distance to next probe
		start codon	*239-241 (Exon 2)*		
256	14340-L16009	Exon 1	119-120	TGGAGAATTGGA-TAGCAGAGTAAT	1.3 kb
382	14352-L16021	Exon 2	173-174	CTTCCGGTCAAA-ATTCACTAGGTA	0.6 kb
148	14325-L16812	Exon 3	367-368	CTCCGCTGCAAT-GCTGAGTACGTA	
		stop codon	*1517-1519 (Exon 4)*		

Table 2b. *SLC40A1* gene

Length (nt)	SALSA MLPA probe	*SLC40A1* exon[a]	Ligation site NM_014585.6	Partial sequence[b] (24 nt adjacent to ligation site)	Distance to next probe
		start codon	*327-329 (Exon 1)*		
427	14356-L16633	Exon 1	261-262	TCCTGTTAACAA-GCACCTCAGCGA	0.7 kb
215	14334-L16003	Exon 2	385-386	CTTGGCCGACTA-CCTGACCTCTGC	4.6 kb
154	14326-L15995	Exon 3	461-462	TGGCACTTTGCG-GTGTCTGTGTTT	2.4 kb
320	14346-L16015	Exon 4	620-621	TCGCTGGTGGTA-CAGAATGTTTCA	1.2 kb
172 Ж	14328-SP0151-L15997	Exon 5	779-780; 815-816	ACTGCTACTGCA-36 nt spanning oligo-GGAGAAGACAGA	6.2 kb
184	14330-L15999	Exon 6	874-875	GATTGACCAGTT-AACCAACATCTT	1.7 kb
143	14324-L15993	Exon 7	1474-1475	ACAGCTTTCCTG-TTTGATCTTGTG	1.8 kb
233 Ж	14337-SP0153-L16006	Exon 8	1846-1847; 1876-1877	TGATCTTCTGCA-30 nt spanning oligo-TGAAGCTTTTGG	
		stop codon	*2040-2042 (Exon 8)*		

Table 2c. *HFE* gene

Length (nt)	SALSA MLPA probe	*HFE* exon[a]	Ligation site NM_000410.4	Partial sequence[b] (24 nt adjacent to ligation site)	Distance to next probe
		start codon	*13-15 (Exon 1)*		
208 Ж	14333-SP0152-L16813	Exon 1	178 nt before exon 1; 145 nt before exon 1	GTGTTTCACAAG-33 nt spanning oligo-AAGTTCTGAAAG	3.6 kb
301	14344-L16013	Exon 2	23 nt before exon 2	CTACACATGGTT-AAGGCCTGTTGC	0.1 kb
244	14338-L16007	Exon 2	144-145	GACCTTGGTCTT-TCCTTGTTTGAA	0.4 kb
160	14327-L15996	Exon 3	1 nt before exon 3	GGGATTTTTCCA-GAGTCCCACACC	0.1 kb
178	14329-L15998	Exon 3	453-454	GACCACCTTGAA-TTCTGCCCTGAC	1.3 kb
419	14355-L16024	Exon 4	2 nt before exon 4	TCTTTCCTGTCA-AGTGCCTCCTTT	0.2 kb
409 § Ж	14354-SP0158-L16030	Exon 4	857-858; 882-883	GAGATATACGTA-25 nt spanning oligo-CAGCCCCTCATT	0.2 kb
346	14348-L16017	Exon 5	912-913	TTAGAGCCCTCA-CCGTCTGGCACC	0.1 kb
221	14335-L16004	Exon 5	981-982	TTGTTCATTGGA-ATTTTGTTCATA	1.2 kb
274 Ж	14342-SP0155-L16011	Exon 6	1192-1193; 1228-1229	AACTCCTTGATT-36 nt spanning oligo-CCATTTAGGTTT	0.1 kb

Length (nt)	SALSA MLPA probe	*HFE* exon[a]	Ligation site NM_000410.4	Partial sequence[b] (24 nt adjacent to ligation site)	Distance to next probe
364 Ж	14350-SP0157-L16019	Exon 6	1302-1303; 1330-1331	TGTCTCTCATGA-28 nt spanning oligo-CATTTCCTCCGT	
		stop codon	*1057-1059 (Exon 6)*		

Table 2d. *TFR2* gene

Length (nt)	SALSA MLPA probe	*TFR2* exon[a]	Ligation site NM_003227.4	Partial sequence[b] (24 nt adjacent to ligation site)	Distance to next probe
		start codon	*44-46 (Exon 1)*		
190	14331-L16000	Exon 1	45-46	GGACACAAGCAT-GGAGCGGCTTTG	0.6 kb
453	14728-L16026	Exon 3	336-337	GCCAGCCTTCCT-ACTGGGCTACGT	7.4 kb
265	14341-L16010	Exon 4	624-625	CGTGTGGACCGA-CACGCACTACGT	1.3 kb
328	14347-L16016	Exon 7	933-934	AGGAGTGCTCAT-ATACCCAGAGCC	2.9 kb
311	14727-L24427	Exon 10	3 nt after exon 10	TGAGCAACGGTA-AGGTCAGGGCCA	1.5 kb
472	14360-L16029	Exon 14	1688-1689	CTCTCTATGAAC-AGGTGGTGTTCA	0.2 kb
226	14336-L16407	Exon 15	1773-1772 *reverse*	GGACTCCCACAA-AGGCCGTGAAGG	6.8 kb
373	14351-L16020	Exon 18	2510-2511	TCCTCGCTTGAA-TGATTCAGGGTC	
		stop codon	*2447-2449 (Exon 18)*		

Table 2e. *HAMP* gene

Length (nt)	SALSA MLPA probe	*HAMP* exon[a]	Ligation site NM_021175.4	Partial sequence[b] (24 nt adjacent to ligation site)	Distance to next probe
		start codon	*51-53 (Exon 1)*		
355 Ж	14349-SP0156-L16018	Exon 1	13-14; 40-41	CCAGAGCAAGCT-27 nt spanning oligo-AGACGGCACGAT	0.1 kb
436 Ж	14729-SP0159-L16028	Exon 1	127-128; 13 nt after exon 1	CAGTGGCTCTGT-27 nt spanning oligo-GCCTGGGTCCTT	2.2 kb
250 Ж	14339-SP0154-L16408	Exon 2	174-175; 198-199	AACCCCAGGACA-24 nt spanning oligo-TGGTGAGCGCAA	0.2 kb
292 ∞	14343-L16012	Exon 3	262-263	TTTCTGCTGCGG-CTGCTGTCATCG	
		stop codon	*303-305 (Exon 3)*		

[a] See section Exon numbering on page 1 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.

§ Mutation-specific probe. This probe will only generate a signal when the C282Y mutation is present. It has been tested on artificial DNA **but not on positive human samples!**

∞ Wild type sequence detected. A lowered probe signal can be due to the G71D mutation. Other variants near the ligation site can also cause a lowered signal. A positive result must be confirmed by another method.
« 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.

Ж This probe consists of three parts and has two ligation sites. A low signal of this probe can be due to depurination of the sample DNA, e.g. due to insufficient buffering capacity or a prolonged denaturation time. When this occurs in reference samples, it can look like an increased signal in the test samples.

SNVs located in the target sequence of a probe can influence probe hybridization and/or probe ligation. Single probe aberration(s) must be confirmed by another method.

References

- Alexander J et al. (2009). HFE-associated hereditary hemochromatosis. *Genet Med*. 11:307-313.
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- Schwartz M et al. (2007). Deletion of exon 16 of the dystrophin gene is not associated with disease. *Hum Mutat.* 28:205.
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- Melo JB et al. (2015). Cutis aplasia as a clinical hallmark for the syndrome associated with 19q13.11 deletion: the possible role for UBA2 gene. *Mol Cytogenet*. 8:21.
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- Ravasi G et al. (2021). Identification of Novel Mutations by Targeted NGS Panel in Patients with Hyperferritinemia. *Genes (Basel)*. 12:1778.

P347 product history	
Version	*Modification*
A3	Three reference probes have been replaced and one reference probe has been removed.
A2	Four reference probes have been replaced and the control fragments have been adjusted (QDX2).
A1	First release.

Implemented changes in the product description
Version A3-02 – 30 August 2022 (04P) - Product description rewritten and adapted to a new template. - Various minor textual or layout changes. - Ligation sites of the probes targeting the HFE2, SLC40A1 and HFE genes updated according to new versions of the NM_ reference sequences. Version A3-01 — 9 December 2019 (02P) - Product description rewritten and adapted to a new template. - Product description adapted to a new product version (version number changed, changes in Table 1 and Table 2). - Ligation sites of the probes targeting the TFR2 and the HAMP genes updated according to new versions of the NM_ reference sequences.

More information: www.mrcholland.com; www.mrcholland.eu	
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