Product Description
SALSA® MLPA® Probemix P478-A2 SMARCE1

To be used with the MLPA General Protocol.

Version A2
As compared to version A1, one probe has a change in length but not in the targeted sequence. For complete product history see page 8.

Catalogue numbers
- **P478-025R:** SALSA® MLPA® Probemix P478 SMARCE1, 25 reactions
- **P478-050R:** SALSA® MLPA® Probemix P478 SMARCE1, 50 reactions
- **P478-100R:** SALSA® MLPA® Probemix P478 SMARCE1, 100 reactions

SALSA® MLPA® Probemix P478 SMARCE1 (hereafter: P478 SMARCE1) is to be used in combination with:

1. SALSA® MLPA® Reagent Kit (Cat. No: EK1-FAM, EK1-CY5, EK5-FAM, EK5-CY5, EK20-FAM),
2. Data analysis software Coffalyser.Net™ (Cat. No: n.a.)

Volumes and ingredients

Volumes			Ingredients
P478-025R	P478-050R	P478-100R	
40 µl	80 µl	160 µl	Synthetic oligonucleotides, oligonucleotides purified from bacteria, Tris-HCl, EDTA

The MLPA probemix 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).

Storage and handling

Recommended storage conditions	-25°C / -15°C	

A shelf life of until the expiry date is guaranteed, 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.

Certificate of Analysis
Information regarding 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
SALSA® MLPA® Probemix P478 SMARCE1 is a **research use only (RUO)** assay for the detection of deletions or duplications in the *SMARCE1* gene, which is associated with familial meningioma and Coffin-Siris syndrome.

Meningiomas are slow-growing tumours that stem from the meninges. They are the most commonly occurring intracranial neoplasms, accounting for up to 30% of all brain tumours (Starr and Cha, 2017). The *SMARCE1*

(Homo sapiens SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily e, member 1) gene encodes a component of the SWI/SNF complex, which modulates eukaryotic gene expression and DNA repair via nucleosome remodelling. Heterozygous *SMARCE1* loss-of-function mutations have been linked to familial meningioma (MIM number 607174). Partial deletions of *SMARCE1* and loss of its expression have been described in spinal meningioma tissue suggesting a tumour suppressor function of this gene (Smith et al. 2013; Smith et al. 2014). Germline mutations in members of SWI/SNF complex, including *SMARCE1*, have been described also in Coffin-Siris syndrome (MIM number 616938) (Tsurusaki et al. 2014).

More information is available at https://www.ncbi.nlm.nih.gov/books/NBK131811/.

This product is not CE/FDA registered for use in diagnostic procedures. The SALSA® MLPA® technique is covered by US patent 6,955,901 and corresponding patents outside the US. The purchase of this product includes a license to use only this amount of product solely for the purchaser's own use.

Gene structure and transcript variants:
Entrez Gene shows transcript variants of each gene: https://www.ncbi.nlm.nih.gov/gene
For NM_ mRNA reference sequences: https://www.ncbi.nlm.nih.gov/nuccore?db=nucleotide
Matched Annotation from NCBI and EMBL-EBI (MANE): https://www.ncbi.nlm.nih.gov/refseq/MANE

Exon numbering
The *SMARCE1* exon numbering used in this P478-A2 SMARCE1 product description is the exon numbering derived from MANE project (v1.4) based on MANE Select transcript NM_003079.5. 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
P478-A2 SMARCE1 contains 37 MLPA probes with amplification products between 130 and 391 nucleotides (nt). This includes 15 probes for the *SMARCE1* gene at 17q21.2, as well as seven flanking probes to help determine the extent of a copy number alteration (CNA) detected in a sample. In addition, 15 reference probes are included that target relatively copy number stable regions in meningioma, as well as in somatic cancer samples in general. Partial probe sequences and the identity of the genes detected by the reference probes are available in Table 3 and 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 MLPA (Schouten et al. 2002) are described in the MLPA General Protocol (www.mrcholland.com). More information on the use of MLPA in tumour applications can be found in Hömig-Hölzel and Savola (2012).

MLPA technique validation
Internal validation using 16 different DNA samples from healthy individuals is required, in particular when using MLPA for the first time, or when changing the sample type or 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, derived from germline blood samples or from tumour tissue and corresponding healthy tissue, which includes DNA derived from formalin-fixed, paraffin-embedded (FFPE) tissues, free from impurities known to affect MLPA reactions. MRC Holland has tested and can recommend the following extraction methods:
- QIAGEN Autopure LS (automated) and QIAamp DNA mini/midi/maxi kit (manual)
- Promega Wizard Genomic DNA Purification Kit (manual)
- Salting out (manual)

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. For more information please refer to the section on DNA sample treatment found in the MLPA General Protocol. More information on the use of FFPE tissue samples for MLPA can be found in Atanesyan et al. (2017).

Reference samples
A sufficient number (≥3) of different reference samples from unrelated individuals should be included in each MLPA experiment for data normalisation. Reference samples for germline analysis should be derived from different unrelated individuals who are from families without a history of Coffin-Siris syndrome and for tumour analysis from different healthy individuals without a history of cancer. 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 ACC-410, ACC-259, and ACC-180 from the Leibniz Institute DSMZ have been tested with P478-A2 SMARCE1 at MRC Holland and can be used as positive control samples to detect a gain of *SMARCE1* gene and its flanking region. The quality of cell lines can change; therefore deviations to the indicated CNA findings might occur.

Sample name	Chromosomal position (hg18) of CNA*	Altered target genes in P478-A2 SMARCE1	Expected CNA
MFE-280 (ACC-410)†	17p13.2-q23.2	*AIPL1, FLCN4, TNS4, CCR7, SMARCE1, KRT222, KRT24,* and *BRIP1*	Gain
HUP-T3 (ACC-259)†	17p13.2	*AIPL1*	Heterozygous deletion
	17q21.2	*TNS4, CCR7, SMARCE1, KRT222,* and *KRT24*	Gain
HEP-G2 (ACC-180)†	17q21.2-q23.2	*TNS4, CCR7, SMARCE1, KRT222, KRT24,* and *BRIP1*	Gain

* Indicated chromosomal bands accommodate genes targeted by MLPA probes, however, the whole extent of CNA present in this cell line cannot be determined by P478-A2 SMARCE1.
† Some of the reference probes are also affected by CNAs.

Data analysis
Coffalyser.Net should be used for data analysis in combination with the appropriate lot-specific Coffalyser sheet. For both, the latest version should be used. Coffalyser.Net 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. When this criterion is 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/gain	1.30 < FR < 1.65
Heterozygous triplication/homozygous duplication/gain	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 Coffalyser.Net (Calculations, cut-offs and interpretation remain unchanged.) Please note that Coffalyser.Net 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.

Please note that these above mentioned final ratios are only valid for germline testing. Final ratios are affected both by percentage of tumour cells and by possible subclonality.

- Arranging probes according to chromosomal location facilitates interpretation of the results and may reveal more subtle changes such as those observed in mosaic cases or subclonal cases.
- 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. single nucleotide variants (SNVs), point mutations) in the target sequence detected by a probe can be one cause. Incomplete DNA denaturation (e.g. due to salt contamination in the DNA sample) 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: https://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.

P481 SMARCE1 specific note:

- In samples from tumour tissues, reference probes are more prone to have deviating copy number results as compared to blood derived germline samples. When regions targeted by reference probes are affected

by CNAs, it can help to turn the slope correction off in Coffalyser.Net analysis to get the correct copy number interpretation on the target region.

Limitations of the procedure

- In most populations, the major cause of Coffin-Siris syndrome-related genetic defects in the *SMARCE1* gene are small (point) mutations, none of which will be detected by using P478 SMARCE1.
- 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.
- MLPA analysis on tumour samples provides information on the *average* situation in the cells from which the DNA sample was purified. Gains or losses of genomic regions or genes may not be detected if the percentage of tumour cells is low. In addition, subclonality of the aberration affects the final ratio of the corresponding probe. Furthermore, there is always a possibility that one or more reference probes *do* show a CNA in a patient sample derived from tumour tissue, especially in solid tumours with more chaotic karyotypes.

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 in sequence data 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.

LOVD, ClinVar, and COSMIC mutation databases

http:// SMARCE1.lovd.nl/genes/
https://www.ncbi.nlm.nih.gov/clinvar/
http://cancer.sanger.ac.uk/cosmic

We strongly encourage users to deposit germline positive results in the LOVD and ClinVar databases and for somatic mutations in the COSMIC database. Recommendations for the nomenclature to describe deletions/duplications of one or more exons can be found on https://varnomen.hgvs.org.

Please report false positive results due to SNVs and unusual results (e.g., a duplication of *SMARCE1* exons 6 and 8 but not exon 7) to MRC Holland: info@mrcholland.com.

Table 1. P478-A2 SMARCE1

Length (nt)	MLPA probe	Chromosomal position (hg18) [a]		Location (hg18) in kb
		Reference	*SMARCE1* and flanking region	
64-105	Control fragments – see table in probemix content section for more information			
130	Reference probe 19616-L26704	4p13		04-042.278
136	Reference probe 17516-L21415	2q32		02-189.569
142	**SMARCE1 probe** 21681-L30338		**Exon 1**	17-036.058
150	Reference probe 10301-L30389	11q14		11-077.639
154	**SMARCE1 probe** 21682-L30339		Upstream	17-036.058
160	Reference probe 16253-L21825	19p13		19-012.779
166	**SMARCE1 probe** 21683-L30340		**Exon 4**	17-036.052
172	Reference probe 08726-L25038	9q21		09-078.038
178	**SMARCE1 probe** 21684-L30341		**Exon 8**	17-036.042
184 Ø	**SMARCE1 probe** 21685-L30342		**Intron 4**	17-036.051
190	Reference probe 18316-L23369	15q24		15-072.494
196	**SMARCE1 probe** 21686-L30343		**Exon 5**	17-036.047
211	Reference probe 15521-L17376	16q13		16-055.505
220 ¬	Flanking probe 06971-L06551		17p13.2	17-006.272
226	**SMARCE1 probe** 21688-L30345		**Exon 2**	17-036.056
232	Reference probe 14739-L30804	4q22		04-089.187
238 ¬	Flanking probe 21689-L30520		17q21.2	17-036.111
244	**SMARCE1 probe** 21690-L30805		**Exon 9**	17-036.041
250 ¬	Flanking probe 08590-L30521		17p11.2	17-017.072
256	Reference probe 05409-L04215	5p13		05-037.012
263	**SMARCE1 probe** 21691-L30348		**Exon 7**	17-036.046
268	**SMARCE1 probe** 21692-L30349		**Exon 11**	17-036.035
274 ¬	Flanking probe 21693-L30781		17q21.2	17-035.966
280	**SMARCE1 probe** 21687-L30780		**Exon 10**	17-036.041
288 ¥	**SMARCE1 probe** 22372-L33138		**Exon 6**	17-036.046
295	Reference probe 20124-L27681	3p12		03-081.667
301	Reference probe 10783-L28289	2p25		02-003.571
310 ¬	Flanking probe 08568-L08569		17q23.2	17-057.294
319	**SMARCE1 probe** 21695-L30352		**Exon 11**	17-036.039
328	Reference probe 07527-L21498	11p13		11-031.773
337	Reference probe 09227-L26255	5q23		05-126.200
346 ¬	Flanking probe 21696-L30353		17q21.2	17-035.895
355 ¬	Flanking probe 21697-L30354		17q21.2	17-036.072
364	**SMARCE1 probe** 21698-L30355		**Exon 3**	17-036.055
373 Ø	**SMARCE1 probe** 21699-L30356		**Intron 10**	17-036.040
382	Reference probe 02459-L01903	15q21		15-046.572
391	Reference probe 10468-L11021	2p11		02-085.636

[a] See section Exon numbering on page 2 for more information.

¥ Changed in version A2. Minor alteration, no change in sequence detected.
¬ Flanking probe. Included to help determine the extent of a deletion/duplication. CNAs of only the flanking or reference probes are unlikely to be related to the condition tested.
Ø Intron probe. Only included to help determine the extent of a deletion/duplication. CNAs of only this probe are of unknown clinical significance.

The probe lengths in the table above may vary slightly depending on the capillary electrophoresis machine settings. Please see the most up-to-date Coffalyser sheet for exact probe lengths obtained at MRC Holland.

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

Table 2. *SMARCE1* and flanking probes arranged according to chromosomal location

Length (nt)	MLPA probe	Gene/exon[a]	Location / Ligation site[b]	Partial sequence (24 nt adjacent to ligation site)	Distance to next probe
220 ¬	06971-L06551	*AIPL1*	17**p**13.2	CGAGGACCTGGA-CGAGCTGCAGAA	10.8 **MB**
250 ¬	08590-L30521	*FLCN*	17**p**11.2	TGGCATTCAGAT-GAACAGTCGGAT	18.8 **Mb**
346 ¬	21696-L30353	*TNS4*	17q21.2	AGAGCAAGGTAA-AAGGAAGCACGA	70.9 kb
274 ¬	21693-L30781	*CCR7*	17q21.2	AAGGTATGCCTG-TGTCAAGATGAG	69.3 kb
SMARCE1, located on 17q21.2. Ligation sites are according to NM_003079.5.					
268	21692-L30349	Exon 11	5050-5051	TTTCTAAGTGTG-AAATGATGGAAC	3.9 kb
		stop codon	*1325-1327 (exon 11)*		
319	21695-L30352	Exon 11	1124-1125	TTACAGAGGAGA-CACACCTTGAAG	1.3 kb
373 Ø	21699-L30356	Intron 10	474 nt after exon 10, reverse	AGGAAAATCAGT-ATACCTAGAAGT	0.7 kb
280	21687-L30780	Exon 10	917-918	AGTTGTGCGGTC-TGAAAGTAGAAG	0.7 kb
244	21690-L30805	Exon 9	898-899	TTTAACAATGAA-CTTAAAAGGGTA	0.8 kb
178	21684-L30341	Exon 8	634-635	TTCACTCCAGAT-TATGATGATGGC	3.6 kb
263	21691-L30348	Exon 7	620-621	TTCAGCCTGCTG-AAGATCCAGATG	0.6 kb
288	22372-L33138	Exon 6	329-330	TTCTTTTTAAGG-TCTGGGACCAAG	1.0 kb
196	21686-L30343	Exon 5	252-253	TTCGTAGGCATC-CTCTGGTATCAC	3.3 kb
184 Ø	21685-L30342	Intron 4	1.5 kb after exon 4	GACTAGGAAGAG-AAAGTGTACTCC	1.5 kb
166	21683-L30340	Exon 4	9 nt after exon 4	ACGGTAGGAGAA-TCAACTATTACA	3.1 kb
364	21698-L30355	Exon 3	1 nt after exon 3	CTCCTGCAACAG-TAAGTTTTAATT	0.2 kb
		start codon	*92-94 (exon 2)*		
226	21688-L30345	Exon 2	81-82	ACTGAGAACTTA-ATCTTCCAAAAT	2.0 kb
142	21681-L30338	Exon 1	9 nt after exon 1	CGGGTGAGTGTT-TCCAAGTGGGAC	0.5 kb
154	21682-L30339	Upstream	433 nt before exon 1	CCAGGAGCGGGC-TCAGCGGGAGTC	13.6 kb
355 ¬	21697-L30354	*KRT222*	17q21.2	CTCTCCATGCTG-TGGTGAGAATGA	39.2 kb
238 ¬	21689-L30520	*KRT24*	17q21.2	CGAGGAGGTAGG-AACATGTTCTAC	21.2 **Mb**
310 ¬	08568-L08569	*BRIP1*	17q23.2	ACGGGTAAGCTT-TATAAGGAAAGT	-

[a] See section Exon numbering on page 2 for more information.
[b] Ligation sites are relative to the start of the NM_ sequence, and not relative to the coding sequence.

¬ Flanking probe. Included to help determine the extent of a deletion/duplication. CNAs of only the flanking or reference probes are unlikely to be related to the condition tested.
Ø Intron probe. Only included to help determine the extent of a deletion/duplication. CNAs of only this probe are of unknown clinical significance.

SNVs located in the target sequence of a probe can influence probe hybridisation 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 3. Reference probes arranged according to chromosomal location

Length (nt)	MLPA probe	Gene	Chromosomal band (hg18)	Partial sequence (24 nt adjacent to ligation site)	Location (hg18) in kb
301	10783-L28289	*RNASEH1*	2p25	TCATTCGGGATT-TATAGGCAATGA	02-003.571
391	10468-L11021	*GGCX*	2p11	TGCGGGTGTGAA-AAAGCTGGATGC	02-085.636
136	17516-L21415	*COL3A1*	2q32	TACTTCAGGGCA-TGCCCGGAAGTC	02-189.569
295	20124-L27681	*GBE1*	3p12	ACCGAGTTGGAA-CAGCATTGCCAG	03-081.667
130	19616-L26704	*ATP8A1*	4p13	CAGATTCTTCTT-CGAGGAGCTCAG	04-042.278
232	14739-L30804	*PKD2*	4q22	CGCATTCACAAA-CTACACTATTTC	04-089.187
256	05409-L04215	*NIPBL*	5p13	CAAGTGCCTGTT-TTACAACAGAAC	05-037.012
337	09227-L26255	*LMNB1*	5q23	AGCACTCTGGAT-GATGGATTCCAC	05-126.200
172	08726-L25038	*PCSK5*	9q21	ACACCTGCCAGA-GATGCCAAGGAA	09-078.038
328	07527-L21498	*PAX6*	11p13	AGTTCCAACGGA-GAAGATTCAGAT	11-031.773

Length (nt)	MLPA probe	Gene	Chromosomal band (hg18)	Partial sequence (24 nt adjacent to ligation site)	Location (hg18) in kb
150	10301-L30389	*GAB2*	11q14	AGCCAGCACCTT-CTCCGAGAGCGC	11-077.639
382	02459-L01903	*FBN1*	15q21	CAGTGTCCCAGT-GGAATGACTTTG	15-046.572
190	18316-L23369	*SEMA7A*	15q24	TACCCACAGAGA-CCTTCCAGGTGG	15-072.494
211	15521-L17376	*SLC12A3*	16q13	GTGCTCACCTTT-TACTGCCAGTAA	16-055.505
160	16253-L21825	*RNASEH2A*	19p13	AGGACACGGACT-TTGTCGGCTGGG	19-012.779

Related products
For related products, see the product page on our website.

References

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Selected publication using P478 SMARCE1

- Smith MJ et al. (2017). SMARCE1 mutation screening in classification of clear cell meningiomas. *Histopathology*. 70:814-20.

P478 product history	
Version	*Modification*
A2	One probe has a change in length but not in the targeted sequence.
A1	First release.

Implemented changes in the product description
Version A2-02 – 19 September 2025 (05P) - Corrections and minor textual changes in *Positive control DNA sample* table on page 3. Version A2-01 – 5 September 2025 (05P) - 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). Version A1-02 – 26 April 2022 (04P) - Product description rewritten and adapted to a new template. - Various minor textual or layout changes. - Ligation sites of the probes targeting the name gene updated according to new version of the NM_003079 reference sequence. Version A1-01 – 13 September 2018 (01P)

- Not applicable, new document.

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