Medicines & Healthcare products Regulatory Agency

NIBSC Confidence in Biological Medicines

CE Marked Material
MLH1/MSH2 Exon Copy Number Reference Panel
NIBSC code: 11/218-XXX
Instructions for use
(Version 11.0, Dated 15/12/2021)

This material is a self certified IVD and complies with the requirements of the "EU in vitro diagnostic medical device directive 98/79/EC"

1. INTENDED USE

This product is CE marked for use as an IVD within the UK, EU member states and EEA countries. In all other territories this product can be used for research purposes only.
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The human genomic DNA materials in the MLH1/MSH2 exon copy number reference panel are intended as single-use controls in multiplex ligation-dependent probe amplification (MLPA)-based dosage analysis of hereditary nonpolyposis colorectal cancer (HNPCC; Lynch Syndrome)-associated mutations in MLH1 (NM_000249.2) and MSH2 (NM_000251.1). The materials are supplied to 'professional users', typically genetic diagnostic laboratories. The materials are intended to act as validators of assay function.
The materials are not for calibration purposes.
The DNA has been extracted using Gentra Puregene chemistries. It should be noted that DNA extracted in this manner may not always be compatibile with local methods.

2. CAUTION

This preparation is not for administration to humans or animals in the human food chain.

Users should establish fitness for purpose by validating the materials on their own platforms.
The panel contains materials of human origin. None of the human genomic DNA materials have been screened for human pathogen presence. All materials were derived from Epstain Barr virus (EBV) transformed lymphoblastoid cell lines. EBV is a category 2 pathogen as classified by the UK Advisory Committee on Dangerous Pathogens. EBV sequences may be present in these materials but the DNA has been prepared using a protocol in which proteins are denatured and removed, thus likely inactivating virus. However, the potential for viable virus to survive cannot be eliminated. As with all materials of biological origin, this preparation should be regarded as potentially hazardous to health. It should be used and discarded according to your own laboratory's safety procedures. Such safety procedures should include the wearing of protective gloves and avoiding the generation of aerosols. Care should be exercised in opening ampoules or vials, to avoid cuts.

3. UNITAGE

Each panel comprises 7 vials of genomic DNA in approximately 50µl Gentra DNA Hydration Solution at a concentration of approximately 100ng/µl.

4. CONTENTS

Country of origin of biological material: United Kingdom.

Each panel contains one vial of genomic DNA of each of the genotypes as listed in Table 1, below.

Each vial is sealed with a differently coloured cap to aid identification. Contact with moisture may reduce the adherance of the vial labels. The cap colours remain the unique identifiers for the tubes' contents.

The panel is intended to provide coverage of MLH1 and MSH2 mutations associated with HNPCC; 5 vials contain deletions/amplifications detected by MLPA, and 2 vials contain point mutations not detected by MLPA (and may serve as as negative controls for this technology).
Customer feedback on genotype coverage is welcomed.

Tube	Cap Colour	Genotype	Patient Sex*
1	Orange	*MLH1* exon 4 c.350C>T (p.Thr117Met) and *MLH1* exon 16 [c.1852A>G;c.1853A>C] (p.Lys618Ala), heterozygous	X, X
2	Green	*MSH2* intron 5 c.942+3A>T, heterozygous	X, Y
3	Purple	*MSH2* deletion exons 1-6, heterozygous	X, X
4	Yellow	*MSH2* deletion exon 7, heterozygous	X, X
5	White	*MSH2* deletion exons 1-2, heterozygous	X, Y
6	Red	*MSH2* deletion exon 1, heterozygous	X, X
7	Blue	*MLH1* exon 13 amplification (three or more copies)	X, Y

Table 1. Genotypes of the seven DNA materials in the MLH1/MSH2 Exon Copy Number Reference Panel. Mutation nomenclature is based on Genbank accession NM_000249.2 (*MLH1*) or NM_000251.1 (*MSH2*) with nucleotide one as the first nucleotide of the translation initiation codon. Nucleotide one (ATGTCGTTCG….) of *MLH1* corresponds to base 36,993,548 of NC_000003.12 Chromosome 3 reference GRCh38. p12 primary assembly; nucleotide one (ATGGCGGTGC…) of *MSH2* corresponds to base 47,403,192 of NC_000002.12 Chromosome 2 reference GRCh38.p12 primary assembly. * Patient sex determined by DNA profiling of Amelogenin.

5. STORAGE

The panel should be stored at -70ºC or below.

6. DIRECTIONS FOR OPENING

Care should be taken to prevent loss of the contents.
Handling in a clean environment in the absence of recombinant plasmid or PCR product is recommended, with the wearing of gloves.
Prior to opening the vials should be briefly centrifuged to ensure the contents are collected at the bottom of the vials. The cap should be removed by anti-clockwise turning. Care should be taken on removal of the cap to prevent loss of contents.

7. USE OF MATERIAL

The materials are intended as controls in MLPA-based dosage analysis of MLH1 and MSH2. Data analysis must be focussed on HNPCC-relevant loci.
DNA concentrations should be determined before use. The materials may require dilution before use; this is dependent on local methodologies and practices.
Do not use if the vial or label is broken. If vials are damaged these materials cannot be used as an In Vitro Diagnostic.

National Institute for Biological Standards and Control,
Potters Bar, Hertfordshire, EN6 3QG. T +44 (0)1707 641000, nibsc.org
WHO International Laboratory for Biological Standards,
UK Official Medicines Control Laboratory

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8. STABILITY (Add or amend as necessary)

Reference materials are held at NIBSC within assured, temperature-controlled storage facilities. Reference Materials should be stored on receipt as indicated on the label.

The expiry date of the panel is shown on the outer container and vial labels. Users who have data supporting any deterioration in the characteristics of any reference material are encouraged to contact NIBSC.

9. REFERENCES

Not applicable

10. ACKNOWLEDGEMENTS

We would like to thank the staff of the UK National Genetics Reference Laboratory, Manchester and CRMGEN consortium for providing materials and assistance.

EC REP Advena Ltd. Tower Business Centre, 2nd Floor, Swatar, BKR 4013, Malta

11. FURTHER INFORMATION

Further information can be obtained as follows;
This material: enquiries@nibsc.org
WHO Biological Standards:
http://www.who.int/biologicals/en/
JCTLM Higher order reference materials:
http://www.bipm.org/en/committees/jc/jctlm/
Derivation of International Units:
http://www.nibsc.org/standardisation/international_standards.aspx
Ordering standards from NIBSC:
http://www.nibsc.org/products/ordering.aspx
NIBSC Terms & Conditions:
http://www.nibsc.org/terms_and_conditions.aspx
NIBSC Genomic Reference Materials:
http://www.nibsc.org/science_and_research/advanced_therapies/genomic_reference_materials.aspx

12. CUSTOMER FEEDBACK

Customers are encouraged to provide feedback on the suitability or use of the material provided or other aspects of our service. Please send any comments to enquiries@nibsc.org

13. CITATION

In all publications, including data sheets, in which this material is referenced, it is important that the preparation's title, its status, the NIBSC code number, and the name and address of NIBSC are cited and cited correctly.

14. MATERIAL SAFETY SHEET (Add or amend as necessary)

Classification in accordance with Directive 2000/54/EC, Regulation (EC) No 1272/2008: Not applicable or not classified

Physical and Chemical properties			
Physical appearance: Clear liquid		Corrosive:	No
Stable:	Yes	Oxidising:	No
Hygroscopic:	No	Irritant:	No
Flammable:	No	Handling:See caution, Section 2	
Other (specify):	Contains material of human origin		

Toxicological properties	
Effects of inhalation:	Not established, avoid inhalation
Effects of ingestion:	Not established, avoid ingestion
Effects of skin absorption:	Not established, avoid contact with skin

Suggested First Aid	
Inhalation:	Seek medical advice
Ingestion:	Seek medical advice
Contact with eyes:	Wash with copious amounts of water. Seek medical advice
Contact with skin:	Wash thoroughly with water.

Action on Spillage and Method of Disposal
Spillage of vial contents should be taken up with absorbent material wetted with an appropriate disinfectant. Rinse area with an appropriate disinfectant followed by water. Absorbent materials used to treat spillage should be treated as biological waste.

15. LIABILITY AND LOSS

In the event that this document is translated into another language, the English language version shall prevail in the event of any inconsistencies between the documents.

Unless expressly stated otherwise by NIBSC, NIBSC's Standard Terms and Conditions for the Supply of Materials (available at http://www.nibsc.org/About_Us/Terms_and_Conditions.aspx or upon request by the Recipient) ("Conditions") apply to the exclusion of all other terms and are hereby incorporated into this document by reference. The Recipient's attention is drawn in particular to the provisions of clause 11 of the Conditions.

16. INFORMATION FOR CUSTOMS USE ONLY

Country of origin for customs purposes*: United Kingdom * Defined as the country where the goods have been produced and/or sufficiently processed to be classed as originating from the country of supply, for example a change of state such as freeze-drying.
Net weight: 35g
Toxicity Statement: Toxicity not assessed
Veterinary certificate or other statement if applicable**.** **Attached:** No