Lynch Syndrome Panel, Sequencing and Deletion/Duplication

Last Literature Review: May 2022 Last Update: September 2023

Lynch syndrome (LS), also known as hereditary nonpolyposis colorectal cancer (HNPCC), is a hereditary cancer syndrome that predisposes individuals to colorectal, endometrial, ovarian, stomach, small bowel, and other cancers. LS is caused by a single pathogenic variant in a mismatch repair (MMR) gene (*MLH1*, *MSH2*, *MSH6*, *PMS2*) or a pathogenic deletion in the *EPCAM* gene leading to *MSH2* inactivation. Cancer type and risk amount depends on the gene in which the pathogenic variant is located (see Cancer Risk by Gene). Biallelic inheritance of two pathogenic variants in a single MMR gene is consistent with a diagnosis of constitutional mismatch repair deficiency (CMMRD), a rare childhood cancer predisposition syndrome characterized by hematologic, brain, and intestinal tumors.

Featured ARUP Testing

To compare directly to other hereditary cancer panels offered by ARUP Laboratories, see the ARUP Hereditary Cancer Panel Comparison table.

Lynch Syndrome Panel, Sequencing and Deletion/Duplication 3001605

Method: Massively Parallel Sequencing/Sequencing/Multiplex Ligation-Dependent Probe Amplification (MLPA)

- Recommended test for individuals with a personal and/or family history consistent with Lynch syndrome when documentation of a causative familial variant is not available
- Testing minors for adult-onset conditions is not recommended; testing will not be performed in minors without prior approval. For additional information, please contact an ARUP genetic counselor at 800-242-2787 ext. 2141.

If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate; refer to the Laboratory Test Directory for additional information.

Disease Overview

Epidemiology

- LS is the most common hereditary colorectal cancer (CRC) syndrome.[1]
  - Approximately 2-4% of CRCs are associated with Lynch syndrome.[1]
- 1 in 279 individuals from the general population are estimated to have Lynch syndrome.[2]

Genetics

Genes

See Genes Tested table for genes included in the panel.

Cancer Risk by Gene

Cancer Type	Cancer Risk by Age 70 (%)				
	MLH1	*MSH2*	*MSH6*	*PMS2*	*EPCAM*
Any	64-78	71-77	28-62	22	Unknown
Colorectum	44-53	42-46	12-20	3	75
Endometrium	35	46	41	13	12
Ovary	11	17	11	3	n/a
Stomach and small bowel	8-16	10-16	2-4	4	n/a
Ureter, kidney	3-4	13-16	2-6	n/a	n/a
Urinary bladder	3-5	7-9	1-4	n/a	n/a
Prostate	7	16	5	5	n/a

n/a, not available

Source: Idos, 2021[3]; Dominguez-Valentin, 2020[4]

Cancer Type	Cancer Risk by Age 70 (%)				
	MLH1	*MSH2*	*MSH6*	*PMS2*	*EPCAM*
Brain	1-2	2-4	1-2	n/a	n/a
Breast (female)	11	13	11	8	n/a

n/a, not available

Source: Idos, 2021[3]; Dominguez-Valentin, 2020[4]

Inheritance

- LS: autosomal dominant
- CMMRD: autosomal recessive

Test Interpretation

Methodology

This test is performed using the following sequence of steps:

- Selected genomic regions, primarily coding exons and exon-intron boundaries, from the targeted genes are isolated from extracted genomic DNA using a probe-based hybrid capture enrichment workflow.
- Enriched DNA is sequenced by massively parallel sequencing (MPS; also known as next generation sequencing [NGS]) followed by paired-end read alignment and variant calling using a custom bioinformatics pipeline.
- Sanger sequencing is performed as necessary to fill in regions of low coverage and in certain situations, to confirm variant calls.
- Long-range PCR followed by nested Sanger sequencing is performed on the following gene and exons:
  - *PMS2* (NM_000535) 11, 12, 13, 14, 15
- Bidirectional Sanger sequencing is performed on the following genes and exons:
  - *MSH2* (NM_000251) 5
  - *PMS2* (NM_000535) 7
- Multiplex ligation-dependent probe amplification (MLPA) is performed on the targeted genes to call exon-level deletions and duplications, including the MSH2 10Mb inversion of exons 1-7.

Clinical Sensitivity

- Variable, dependent on gene[5]
  - Greater than 80% for the *MLH1* and *MSH2* genes
  - Unknown for the *MSH6* and *PMS2* genes
- Proportion of Lynch syndrome attributed to pathogenic variants in specific MMR gene[3]:
  - *MLH1*: 15-40%
  - *MSH2*: 20-40%
  - *MSH6*: 12-35%
  - *PMS2*: 5-25%
  - *EPCAM*: <10%

Analytic Sensitivity

- For Sanger sequencing and multiplex ligation-dependent probe amplification (MLPA) of *PMS2*: 99%
- For MLPA of *MLH1*, *MSH2*, *MSH6* deletions/duplications, and *EPCAM* exon 9 deletions: 99%
- For massively parallel sequencing:

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region	Analytic Sensitivity (NPA) Estimate (%)
SNVs	>99 (96.9-99.4)	>99.9

[a]PPA values are derived from larger methods-based MPS and/or Sanger validations.

[b]Variants greater than 10 bp may be detected, but the analytic sensitivity may be reduced.

bp, base pairs; NPA, negative percent agreement; PPA, positive percent agreement; SNVs, single nucleotide variants

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region	Analytic Sensitivity (NPA) Estimate (%)
Deletions 1-10 bp[b]	93.8 (84.3-98.2)	>99.9
Insertions 1-10 bp[b]	94.8 (86.8-98.5)	>99.9
Exon-level deletions/duplications (MLPA)	>99	>99.9

[a]PPA values are derived from larger methods-based MPS and/or Sanger validations.

[b]Variants greater than 10 bp may be detected, but the analytic sensitivity may be reduced.

bp, base pairs; NPA, negative percent agreement; PPA, positive percent agreement; SNVs, single nucleotide variants

Contraindications for Ordering

- Should not be ordered to detect somatic variants associated with malignancy because sensitivity for mosaic variants is low when using the methodology for germline assays
- Individuals with hematologic malignancy and/or a previous allogenic bone marrow transplant should not undergo molecular genetic testing on peripheral blood specimen.
  - Testing of cultured fibroblasts is required for accurate interpretation of test results.

Results

Result	Variant Detected	Clinical Significance
Positive	One pathogenic variant detected	Consistent with a diagnosis of Lynch syndrome/hereditary nonpolyposis colorectal cancer (HNPCC)
Negative	No pathogenic variants detected	Diagnosis of Lynch syndrome/hereditary nonpolyposis colorectal cancer (HNPCC), is unlikely but not excluded; does not exclude another hereditary cancer syndrome
Inconclusive	Variant of uncertain clinical significance detected	Uncertain; it is unknown whether variant is benign or pathogenic

Limitations

- A negative result does not exclude Lynch syndrome or a heritable form of cancer.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if this individual has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of the targeted genes
  - Regulatory region variants and deep intronic variants
  - Breakpoints of large deletions/duplications
  - Sequence variants in *EPCAM*
  - Noncoding transcripts
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Single exon deletions/duplications based on the breakpoints of the rearrangement
  - Low-level somatic variants
  - Single exon deletions/duplications in the following exons:
    - *MLH1* (NM_000249) 12
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions

Genes Tested

To compare directly to other hereditary cancer panels offered by ARUP Laboratories, see the ARUP Hereditary Cancer Panel Comparison table.

Gene	MIM Number	Disorder/Associated Cancer(s)/Tumor(s)	Inheritance
MLH1	120436	Lynch syndrome/HNPCC Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, small bowel, and others	AD
		CMMRD	AR
MSH2	609309	Lynch syndrome/HNPCC Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, small bowel, and others	AD
		CMMRD	AR
MSH6	600678	Lynch syndrome/HNPCC Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, small bowel, and others	AD
		CMMRD	AR
PMS2	600259	Lynch syndrome/HNPCC Associated cancer(s)/tumor(s): colorectal, endometrial, stomach, ovarian, small bowel, and others	AD
		CMMRD	AR
EPCAM	185535	Lynch syndrome/HNPCC Associated cancer(s)/tumor(s): colorectal and endometrial	AD

AD, autosomal dominant; AR, autosomal recessive

References

1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: genetic/familial high-risk assessment—colorectal. Version 1.2021. Updated May 2021; accessed Nov 2021.

2. Win AK, Jenkins MA, Dowty JG, et al. Prevalence and penetrance of major genes and polygenes for colorectal cancer. *Cancer Epidemiol Biomarkers Prev*. 2017;26(3):404-412.

3. Idos G, Valle L. Lynch syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. *GeneReviews.* University of Washington, Seattle. Last revision Feb 2021; accessed Nov 2021.

4. Dominguez-Valentin M, Sampson JR, Seppälä TT, et al. Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. *Genet Med*. 2020;22(1):15-25.

5. Hegde M, Ferber M, Mao R, et al. ACMG technical standards and guidelines for genetic testing for inherited colorectal cancer (Lynch syndrome, familial adenomatous polyposis, and MYH-associated polyposis). *Genet Med*. 2014;16(1):101-116.

Related Information

Lynch Syndrome - Hereditary Nonpolyposis Colorectal Cancer (HNPCC)
Lynch Syndrome (HNPCC) Testing Algorithm
Hereditary Cancer Germline Genetic Testing

ARUP Laboratories is a nonprofit enterprise of the University of Utah and its Department of Pathology. 500 Chipeta Way, Salt Lake City, UT 84108
(800) 522-2787 | (801) 583-2787 | aruplab.com | arupconsult.com