Genomic Diagnostics

LEADING THE WAY TO IMPROVE HEALTH

Familial Colorectal Cancer

CLINICIAN GUIDE FOR GENOMIC TESTING

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Familial Colorectal Cancer Guide for Genomic Testing

Colorectal cancer is the third most common type of newly diagnosed cancer in Australia. It is estimated that 30% of patients with colorectal cancer have a family history of the disease, and up to 10% have genomic variants associated with inherited cancer syndromes including Lynch syndrome and familial adenomatous syndromes FAP and MAP.

MBS rebated diagnostic and predictive testing for the genes associated with these syndromes is now available for patients who meet criteria and when requested by a specialist medical practitioner.

Lynch syndrome (LS)

LS is one of the most common cancer predisposition syndromes, and confers a significantly increased lifetime risk of colorectal cancer (CRC), endometrial cancer (EC) and multiple other cancers.

LS should be suspected in patients with CRC/EC and one or more of the following: personal history of multiple LS related cancers, CRC/EC prior to age 50, or a family history of LS related cancers. It should also be suspected when there is evidence of MMR deficiency on analysis of tumour tissue, or there is a known family pathogenic variant associated with LS.

A diagnosis of LS is confirmed by the detection of a pathogenic germline variant in one of the MMR genes *(MLH1, MSH2, MSH6* and *PMS2)* or the *EPCAM* gene.

Familial adenomatous polyposis (FAP)

FAP is an autosomal dominant disorder characterised by numerous (>100 to 1000s) gastrointestinal adenomatous polyps that almost inevitably progress to CRC by age 40, and a wide array of extra-intestinal lesions involving various organs. A variant of the disorder, attenuated FAP, has a later onset, fewer polyps (usually <100) and reduced occurrence of extra-intestinal manifestations.

Both forms of FAP are caused by pathogenic variants of the *APC* gene. Up to one third of cases are due to de novo (new) variants and therefore have no family history of disease.

About 70% of FAP cases and 25% of attenuated FAP cases will have an *APC* pathogenic variant identified. Some patients without an identifiable *APC* variant will have biallelic pathogenic variants in *MUTYH*.

MUTYH-associated polyposis (MAP)

MAP is an autosomal recessive disorder characterized by attenuated adenomatous colorectal polyposis (usually 15-100 polyps) and significantly increased lifetime risk of colorectal cancer. Extra-colorectal manifestations can also occur, including duodenal adenomatous polyps associated with an increased risk of duodenal adenocarcinoma, and skin lesions. Colorectal cancer in MAP can also occur rarely in the absence of polyposis. Due to the recessive nature of MAP, there may not be a family history of clinical disease.

MAP is caused by biallelic pathogenic variants of the *MUTYH* gene. These inherited variants predispose to the development of somatic *APC* pathogenic variants in the gastrointestinal tract.

Genomic testing for inherited CRC syndromes

Detection of pathogenic variants in genes associated with inherited colorectal cancer syndromes:

- confirms a diagnosis in patients with a personal history of cancer
- provides genotype-specific information on lifetime risk of cancers
- directs patient management, including surveillance and consideration of prophylactic surgery, based on genotype-specific risks
- guides testing of at-risk (asymptomatic) family members

Diagnostic testing

Guidelines recommend testing to confirm the diagnosis of an inherited CRC syndrome in a patient with a personal history of disease in the following circumstances:

- LS five gene testing is indicated when there is evidence of MMR deficiency and no *BRAF* variant or hypermethylation of *MLH1* in tumour tissue, a known family pathogenic variant, or ≥5% chance of LS based on risk prediction models.
- *APC* gene testing is indicated in patients with ≥10 colorectal adenomas before age 30, or ≥20 colorectal adenomas regardless of age.
- *MUTYH* gene testing is indicated for patients with ≥20 colorectal adenomas at any age, but could also be considered in patients with fewer polyps following review by a familial cancer service, and patients with an FAP phenotype but no identifiable *APC* variant.

Predictive testing

Testing can be offered to individuals without clinical features of an inherited CRC syndrome, to enable appropriate surveillance and preventive management.

Testing should be offered when there is a known family pathogenic variant in one of the five LS associated genes, the *APC* gene, or the *MUTYH* gene.

When family variant information is unavailable, LS five gene testing could also be considered in individuals without a personal history of cancer for whom there is ≥5% chance of LS based on risk prediction models.

Predictive testing is best performed in consultation with a familial cancer service and must be provided with pre- and post-test genetic counselling.

Risk prediction models

Strategies to identify individuals at risk of LS or individuals who should have germline testing for LS have evolved over time. Prediction models are evidence-based tools that use personal and family history to determine the risk that an individual is a carrier of a pathogenic variant in a gene associated with LS. These models can be used in patients with or without a personal history of CRC or EC and are summarized in the table below.

RISK CALCULATOR	SOURCE	BACKGROUND
PREMM5 Available online at: https://premm.dfci.harvard.edu/	Hereditary GI cancer risk and prevention program at New York – Presbyterian Hospital/Columbia University Medical Centre, USA	The model predicts an individual's risk of carrying a pathogenic variant in five genes associated with LS. The only clinical prediction model to include risk assessment for *PMS2* and *EPCAM* genes. Input includes personal and family history of CRC and EC.
MMR Pro	Dept. of Environmental Health Sciences & Dept. of Biostatistics, John Hopkins Bloomberg School of Public Health, USA	This model predicts the chance of a pathogenic sequence variant or large rearrangement in *MLH1/MSH2/MSH6*, as well as the yearly probability of developing CRC and/or endometrial cancer for the proband (if asymptomatic). Input includes personal and family history of CRC and EC, and optional tumour MSI/IHC and family pathogenic variant information.
MMR Predict	Colon Cancer Genetics Group, School of Molecular & Clinical Medicine, University of Edinburgh, UK	This model predicts the chance of a pathogenic sequence variant in *MLH1/MSH2/MSH6* or a large rearrangement in *MLH1/MSH2*.

Guidelines recommend anyone with a risk ≥5% calculated by these models have germline testing however, MBS guidelines require a risk ≥10%. Careful consideration of the patient's personal and family history is necessary to determine which model should be used and what characteristics about a patient's history may limit the interpretation of the risk assessment.

A note on *BRAF* and *MLH1* promoter methylation testing.

International guidelines recommend universal testing of CRC and EC for MMR deficiency, performed by IHC or microsatellite instability testing, as a preliminary screen for LS.

However, most MMR deficient CRC/EC is not due to LS, but the result of acquired silencing of the *MLH1* gene in the tumour. This can be differentiated directly by methylation testing of the tumour tissue to detect *MLH1* gene silencing, or indirectly by testing for the *BRAF V600E* variant, which is found frequently in tumours with *MLH1* promoter methylation but almost never in LS.

Testing options available

Australian and international guidelines for diagnosis, treatment and surveillance of inherited CRC syndromes are available and should be consulted when requesting genomic testing and making clinical decisions for your patient.

TEST	DESCRIPTION	DETAIL
Lynch Syndrome Gene Panel *(MLH1, MSH2, MSH6, PMS2, EPCAM)*	Multi-gene test analyses the mismatch repair (MMR) genes and *EPCAM* gene which cause Lynch syndrome.	Investigation of Lynch Syndrome in patients with colorectal cancer or endometrial cancer where there is a familial risk of ≥10%. The test is bulk billed for patients who fit the criteria under Medicare item 73354.
FAP Gene Panel *(APC, MUTYH)*	Gene test analysing *APC* and *MUTYH* genes which cause FAP and *MUTYH*-associated polyposis.	Investigation of FAP/MAP in patients with adenomatous polyposis and who have a familial risk of ≥10%. The test is bulk billed for patients who fit the criteria under Medicare item 73355.
Colorectal Cancer Predictive Test	For specified familial pathogenic variants for either Lynch Syndrome or FAP/MAP.	Testing of patients with a known familial pathogenic variant. This is bulk billed at no cost to patients under Medicare item 73357.

All genes except EPCAM are assessed for both sequence level and copy number variants.
EPCAM is assessed for copy number variants in selected regions of the gene.

Genetic Counselling

Genetic counselling is of benefit to all patients undergoing cancer gene testing. It involves discussing the potential benefits, limitations and possible consequences of the genomic testing to be performed. Genetic counselling can be provided by the referring specialist or a qualified genetic counsellor.

For patients eligible for MBS Item Number 73354 or 73355, Genomic Diagnostics can facilitate pre-test counselling through Genetic Counselling Australia at no cost to the patient. Please ensure the appropriate box is ticked on the request form if this service is required.

Where the patient is not eligible for these item numbers, and a referral to a genetic counsellor is preferred, Genomic Diagnostics can facilitate this at an affordable cost to the patient.

How to Order

STEP 1: Patient Consultation:

- Use the Genomic Diagnostics Cancer Genetics request form
- Tick the relevant boxes for Test Requested and Medicare eligibility and indicate clinical condition
- Take note of any special conditions listed below for the appropriate panel
- Ensure that the patient understands the implications of undergoing gene testing. If genetic counselling is performed inhouse, ensure Patient Consent section on the reverse of the Cancer Genetics request form is signed.

STEP 2: Prepare for Collection

- If the patient is not eligible for Medicare, prepayment via genomicdiagnostics.com.au is required
- Patient notes their receipt number on the request form.

STEP 3: Sample collection

- Patient attends collection centre with signed request form
- Blood collected
- Familial colorectal cancer genomic testing performed.

STEP 4: Result Discussion

- Results are returned using your preferred method
- Arrange appropriate genetic counselling if a pathogenic variant is detected.

Medicare item 73354 – diagnostic testing for Lynch syndrome in individuals with colorectal or endometrial cancer

The Lynch syndrome gene panel qualifies for the use of this rebate.
Special Conditions:
1. In colorectal cancer, if patient has loss of MMR protein via IHC in solid tumour tissue
2. If patient has endometrial cancer, assess if patient risk of having Lynch syndrome is >10% using a risk calculator model.

MBS Item Descriptor

Characterisation of germline gene variants, including copy number variation, in the *MLH1, MSH2, MSH6, PMS2* and *EPCAM* genes, requested by a specialist or consultant physician, for: (a) a patient with suspected Lynch syndrome following immunohistochemical examination of neoplastic tissue that has demonstrated loss of expression of one or more mismatch repair proteins; or (b) a patient: (i) who has endometrial cancer; and (ii) who is assessed by the specialist or consultant physician as being at a risk of more than 10% of having Lynch syndrome, on the basis of clinical and family history criteria.

Medicare item 73355 – diagnostic testing in individuals with FAP/MAP

The FAP gene panel qualifies for the use of this rebate
Special Conditions:
1. Assess if the patient risk of having FAP or MAP is >10% using a risk score calculator.

MBS Item Descriptor

Characterisation of germline gene variants, including copy number variation, in the *APC* and *MUTYH* genes, requested by a specialist or consultant physician, for a patient: (a) who has adenomatous polyposis; and (b) who is assessed by the specialist or consultant physician as being at a risk of more than 10% of having either of the following, on the basis of clinical and family history criteria: (i) familial adenomatous polyposis; (ii) MUTYH associated polyposis.

Medicare item 73357 – familial testing

The Colorectal Cancer Predictive Test qualifies for the use of this rebate
Special Conditions:
1. Include the pathogenic variants identified in the first degree relative on the request form.
2. Please note that testing is not offered for genes covered by item 73356.

MBS Item Descriptor

Characterisation of germline gene variants, including copy number variation, in the genes mentioned in item 73354, 73355 or 73356, requested by a specialist or consultant physician, for a patient:
(a) who has a biological relative with a pathogenic mutation identified in one or more of those genes; and
(b) who has not previously received a service to which any of items 73354, 73355 and 73356 apply item.

References

Biller et al 2019, PMID 30627969. Giardiello et al 2014, PMID 25003300. Gupta et al 2019, PMID 31487681. Dinarvand et al 2019, PMID 31070935.
Menahem et al 2020, (PMID 32113818. Syngal et al 2015, PMID 25645574. Clinical practice guidelines for the prevention, early detection and management of colorectal cancer. Available at: https://wiki.cancer.org.au/australia/Guidelines:Colorectal_cancer. Monahan et al 2020, PMID 31780574.
Requirements for medical testing of human nucleic acids. Available at: https://www1.health.gov.au/internet/main/publishing.nsf/Content/health-npaac-publication.htm.
Yurgelun et al 2018, PMID 30231390. Kastrinos et al 2017, PMID 28489507. Chen et al 2006, PMID 17003396. Barnetson et al 2006, PMID 16807412.

Why Genomic Diagnostics?

Our extensive experience:

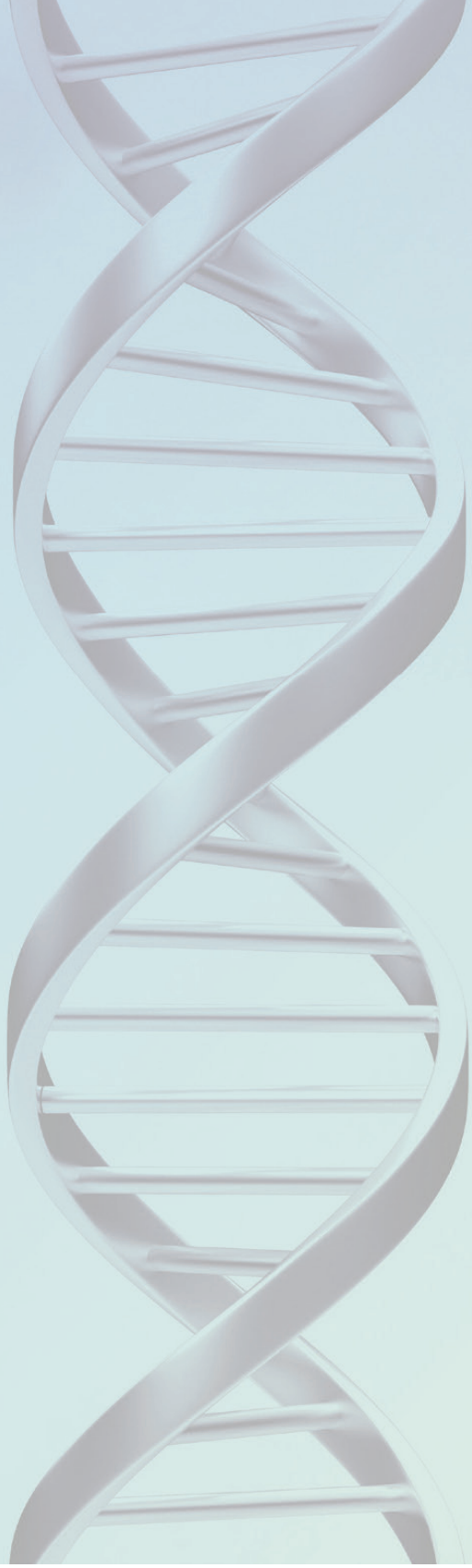
- With more than 10 years' experience in diagnostic genomics we are your reliable partner for genomic testing

We are responsive:

- We are committed to delivering the fastest possible turnaround times
- Our dedicated and knowledgeable customer care team are available to assist you and address your queries

Our commitment to quality is reflected in our testing service:

- We are NATA/RCPA accredited for diagnostic genomic testing
- We participate in regular external quality assurance programs for all tests
- We welcome your queries and are happy to discuss test results and interpretation
- Our expert staff are highly skilled in interpretation of genomic results



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For more information, contact us at info@genomicdiagnostics.com.au

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