



Australian Government
Medical Services Advisory Committee

Public Summary Document

Application No. 1504 - Heritable mutations which increase risk in colorectal and endometrial cancer

Applicant: The Royal College of Pathologists of Australasia (RCPA)

Date of MSAC consideration: MSAC 73rd Meeting, 26-27 July 2018

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

1. Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing for genetic testing to identify inheritable mutations predisposing to colorectal and endometrial cancer, specifically the identification of heritable mutations associated with the clinical presentations of Lynch Syndrome (LS), Familial Adenomatous Polyposis (FAP), MUTYH-Associated Polyposis (MAP), Juvenile Polyposis Syndrome (JPS), Peutz-Jeghers Syndrome (PJS), and Hereditary Mixed Polyposis Syndrome (HMPS), was received from the RCPA by the Department of Health.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC deferred its advice on MBS funding of genetic testing to identify heritable mutations predisposing to colorectal and endometrial cancer, specifically the mutations associated with the clinical presentations of LS, FAP, MAP, JPS, PJS and HMPS.

MSAC acknowledged that germline genetic testing of patients with colorectal or endometrial cancer is now standard care. MSAC accepted the clinical and cost-effectiveness evidence for LS and for FAP, and considered it was reasonable to also include the requested testing of additional genes to detect mutations associated with the identified rarer syndromes associated with colorectal or endometrial cancer in the new MBS items by relying on this same evidence base.

MSAC deferred its advice to request revision of each of the proposed MBS items (i.e. for diagnostic testing and for cascade testing) into three items (with the item descriptors to be based around (a) Lynch Syndrome [*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*], (b) familial adenomatous polyposis [*APC*, *MUTYH*], and (c) the other identified syndromes grouped under familial non-adenomatous polyposis [*SMAD4*, *BMPRIA*, *STK11*, *GREM1*]), and for the further investigation of an appropriate fee for each of the three diagnostic testing MBS items.

The resubmission should also include a breakdown of costs and utilisation reflecting this rearrangement.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that the proposed purposes and populations are (a) diagnostic testing of patients with either (i) colorectal or endometrial carcinoma and features suggestive of a hereditary basis, or (ii) a colonic polyposis syndrome, plus (b) cascade testing of relatives of those individuals who are diagnosed with the relevant germline gene variants. The diagnostic genetic test is to characterise germline gene variants in three or more of the most commonly involved genes (*APC*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *MUTYH*), with or without testing of additional genes (including *SMAD4*, *BMPRIA*, *STK11*, *GREM1* and *EPCAM*).

The aim of the diagnostic genetic test is to improve identification of people at greater risk of developing colorectal and endometrial cancer and allow for appropriate change in management to prevent progression of disease. This would result in an increased number of people requiring early surgical intervention and entering surveillance programs, and a decreased number of people requiring later-stage surgical treatment and chemotherapy. The number of unnecessary referrals for screening colonoscopy would also decrease, as approximately half of the targeted population for testing would revert to the general population risk because they do not carry the disease-causing genetic variant.

MSAC noted that the application had been considered by the Predisposition Genetic Testing Working Group but not by PICO Advisory Sub-Committee (PASC). MSAC acknowledged that the application may have benefited from PASC consideration.

The comparator clinical pathway was largely accepted as 'no testing', although MSAC noted that the comparator for LS in the model was 'immunohistochemistry + no genetic testing'. MSAC considered this to be appropriate, as current guidelines (Cancer Council Australia 2017 and NICE 2017) indicate that all colorectal cancers should undergo immunohistochemistry to detect mismatch repair proteins as a first step. MSAC also acknowledged that germline genetic testing of selected patients with colorectal or endometrial cancer is now standard care.

MSAC considered that the MBS item descriptor required amendments to better define the gene combinations and gene numbers to be tested. The open definition in the proposed item descriptor would allow multiple gene combinations to be tested, but the modelling assumes that a minimum set would be tested. In addition, since immunohistochemistry for mismatch repair protein is performed first, and if the requirement for previous immunochemistry is added to the item descriptor, then the proposed text of '[for a patient] for whom clinical and family history criteria, as assessed by a treating specialist, place the patient at a >10% risk of having a clinically actionable pathogenic mutation' for suspected LS probands could be removed. MSAC suggested revising the item descriptors as follows:

For suspected LS probands:

- Item 1: Characterisation of germline gene variants, requested by a specialist or consultant physician, in all of the following genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*) in a patient with non-polyposis colorectal cancer, following immunohistochemical examination of biopsy material that has demonstrated abnormal (non-somatic) mismatch repair protein expression.
- Item 2: Characterisation of germline gene variants, requested by a specialist or consultant physician, in all of the following genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*) in a patient with endometrial cancer, for whom clinical and family history

criteria, as assessed by the specialist or consultant physician who requests the service, place the patient at >10% risk of having Lynch syndrome.

For suspected familial polyposis probands:

- Item 3: Characterisation of germline gene variants, requested by a specialist or consultant physician, in all of the following genes (*APC* and *MUTYH*) in a patient with adenomatous polyposis, for whom clinical and family history criteria, as assessed by the specialist or consultant physician who requests the service, place the patient at >10% risk of having familial adenomatous polyposis or *MUTYH*-associated polyposis.
- Item 4: Characterisation of germline gene variants, requested by a specialist or consultant physician, in all of the following genes (*SMAD4*, *BMPRIA*, *STK11*, and *GREM1*) in a patient with non-adenomatous polyposis, for whom clinical and family history criteria, as assessed by the specialist or consultant physician who requests the service, place the patient at >10% risk of having juvenile polyposis syndrome, Peutz-Jeghers syndrome or hereditary mixed polyposis syndrome.

MSAC considered that the proposed revisions to the item descriptors, including the associated item for cascade testing, could be completed by the Department with support from the MSAC Executive. MSAC also requested the Department to investigate the fees currently charged by laboratories for this service to help define the proposed fees, which would be expected to vary across the four diagnostic testing items given the substantial difference in numbers and sizes of genes to be tested. In this regard, MSAC noted the relatively large size of the *PMS2* gene.

Regarding comparative safety, MSAC considered that the test itself was safe as it would be performed on a blood sample or archival tissue sample. However, there are potential flow-on effects – the more genes that are tested, the greater the likelihood that incidental findings and variants of unknown significance (VUS) will be detected, which may lead to patient anxiety, unnecessary screening or unnecessary preventive surgery. MSAC noted that LS and FAP have strong clinical presentations that would override genetic testing if there were discordant test results.

MSAC noted that the bulk of the evidence presented in the application was for LS and FAP. However, MSAC acknowledged that data are very limited for JPS, PJS and HMPS, and further relevant data are unlikely to be generated. MSAC accepted the clinical and cost-effectiveness evidence for LS and for FAP, and considered it was reasonable to also include the requested testing of additional genes to detect mutations associated with the identified rarer syndromes associated with colorectal or endometrial cancer in the new MBS items by relying on this same evidence base.

The economic evaluation modelled LS and familial polyposis (FAP and MAP) separately and did not include modelling for the other genes. MSAC considered that this was appropriate – separate models for LS and FAP are more informative and can be more directly linked to funding decisions. Combining these into a single model would not be appropriate due to differing populations, health states, use of risk-reducing surgery and transition probabilities.

Both models assumed no change in management for the proband associated with genetic testing, and all clinical utility accrued to biological relatives. However, MSAC considered this to be an underestimate, as benefits will also accrue to both the proband and to tested patients who are shown not to have an elevated genetic risk. For proband testing, the cost per mutation detected was \$9762 for LS and \$5691 for FAP. For cascade testing, the test was cost-saving or cost-effective across most scenarios.

The application presented a single combined financial impact assessment of genetic testing costs only, which MSAC considered created difficulties in estimating downstream costs and cost offsets. MSAC advised that financial estimates should be compared and triangulated with assumptions used in the economic model to ensure consistency and adjusted for the varying fees and expected numbers of diagnostic and cascade tests across each of the revised MBS items. MSAC accepted that the financial estimates were reasonable, and so advised that the existing model did not need any major changes, but that its identified minor issues should be addressed in a resubmission.

Overall, MSAC considered that the application was complex, with a range of distinct clinical syndromes (with different cancer risks and clinical management pathways) linked to particular genes, and no uniform ‘star performer’ gene. MSAC advised that the application should be reframed with a clinical perspective by splitting the groups into LS/nonpolyposis (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*), familial adenomatous polyposis (*APC*, *MUTYH*), and familial non-adenomatous polyposis (*SMAD4*, *BMPRIA*, *STK11*, *GREM1*). The resubmission should also include a breakdown of costs and utilisation reflecting this rearrangement.

MSAC requested that any resubmission be provided to the MSAC Executive.

MSAC noted that the Clinical Utility Card (CUC) proforma would be further developed following further insights obtained through this and related applications, and following further advice from Predisposition Genetic Testing Working Group.

4. Background

MSAC has not previously considered this application.

5. Prerequisites to implementation of any funding advice

Genetic testing must be performed in laboratories that have received National Association of Testing Authorities (NATA) accreditation.

6. Proposal for public funding

The proposed item descriptors are summarised in Table 1.

Table 1 Proposed MBS item descriptor

Category 6 – (Group P7 Genetics) – Pathology services
Characterisation of germline gene variants in three or more of the following <i>genes APC, MLH1, MSH2, MSH6, PMS2, MUTYH</i> with or without any of these genes <i>SMAD4, BMPRIA, STK11, GREM1, and EPCAM*</i> [*deletions associated with epigenetic silencing of <i>MSH2</i>], in a patient with colorectal or endometrial cancer, or familial polyposis syndrome, for whom clinical and family history criteria, as assessed by a treating specialist place the patient at >10% risk of having a clinically actionable pathogenic mutation identified. MBS Fee: \$1200Benefit: 75% = \$900, 85% = \$1020
Category 6 – (Group P7 Genetics) – Pathology services
Request by a clinical geneticist, or a medical specialist providing professional genetic counselling services, for the detection of a clinically actionable pathogenic mutation previously identified in a gene listed in Item XXXXX in a relative. MBS Fee: \$400Benefit: 75% = \$300, 85% = \$340

7. Summary of Public Consultation Feedback/Consumer Issues

A letter supporting this application was received from a professional organisation.

8. Proposed intervention's place in clinical management

FAP, JPS, Lynch syndrome (formerly known as hereditary nonpolyposis colorectal cancer (HNPCC)), PJS, HMPS and autosomal recessive colorectal adenomatous polyposis (*MUTYH*-associated polyposis or MAP) are all inheritable syndromes predisposing to colorectal and other epithelial cancers.

The genetic testing includes colorectal cancer (CRC) with evidence of mismatch repair (MMR) deficiency and/or clinical evidence of a possible familial polyposis syndrome; and cascade testing of family members of patients identified with clinically actionable pathogenic mutations on the request of a medical specialist or clinical geneticist.

The proposed genes for testing are: *APC*, *SMAD4*, *BMPRIA*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *STK11*, *GREM1*, *MUTYH*, and *EPCAM** [*deletions associated with epigenetic silencing of *MSH2*].

Generally for the gastrointestinal (GI) cancer predisposition genes, those testing positive require close surveillance with colonoscopy to detect the rapidly growing cancers which occur driven by, for example, the mutator phenotype (accumulating hundreds of mutations in the tumours) typically of Lynch Syndrome.

Those who do develop colorectal cancer are usually advised to have extensive rather than limited, oncological resections, to reduce their risk of metachronous cancer. On the other hand, those family members testing negative for the family specific mutation need no special surveillance and, if otherwise of average risk, can join the immunochemical faecal occult blood test (iFOBT)-based National Bowel Cancer Screening Program. If other factors place them at higher than average risk, they should be managed as appropriate for that circumstance.

If genetic testing has not been undertaken, all family members would need to remain under colonoscopic surveillance in case they had inherited the family specific mutation in the relevant gene.

If genetic testing is undertaken, disease management of mutation positive family members would follow clinical management recommendations respective to the disease. Mutation negative family members would revert to general population risk and follow guidelines for screening of the general population.

9. Comparator

The application stated that the target population 'currently undergoes no genetic testing. 'No testing' is the nominated comparator.

10. Comparative safety

The relative safety of performing the proposed gene testing versus the main comparator primarily focused on the presentation of 'flow on' safety consequences that arise as a result of conducting the proposed services. It did not consider the immediate or delayed safety consequences of physically performing the service given the low risk nature of the blood collection to obtain a sample to conduct the test.

11. Comparative effectiveness

In broad terms, the following benefits are expected through offering the proposed gene testing (primarily the benefits to mutation positive family members of the two more common conditions are summarised here). The application attempts to provide evidence to back up these claims.

Lynch syndrome

Colorectal

- increased life expectancy
- significant reduction of bowel cancer risk equivalent to general population risk through more intensive surveillance

Endometrial and ovarian

- hysterectomy and risk reducing salpingo-oophorectomy (RRSO) are interventions which significantly reduce the risk of both endometrial and ovarian cancer

Familial adenomatous polyposis

- systematic reviews have found that registration in dedicated registers, surveillance and colectomy are associated with a consistent and significant reduction in incidence and CRC-related mortality

12. Economic evaluation

Stepped results of the economic analyses of the proposed listings were presented; firstly for the initial diagnostic testing in index cases, then secondly, with the addition of familial testing for known mutations.

Given the populations suspected for Lynch syndrome and familial polyposis are clinically distinct, the cost-effectiveness of genetic testing and familial testing for these conditions have been modelled separately. The larger of the populations are the suspected Lynch syndrome patients (representing approximately 3 to 6% of colorectal cancer patients), whereas the familial polyposis population is smaller (less than 1% of colorectal cancer patients).

The cost-effectiveness of testing for index cases of Lynch syndrome is presented in Table 2. There is no evidence of direct clinical outcomes associated with genetic diagnosis of index cases, however the outcome ‘identification of mutation’, is relevant as this enables downstream familial testing which does effect both health outcomes and costs.

Table 2 Cost-effectiveness of diagnostic genetic testing vs no testing for index cases with Lynch syndrome

Strategy	Cost	Mutations identified
Diagnostic genetic testing for Lynch syndrome	\$1,596	16%
No genetic testing	\$0	0%
Increment	\$1,596	16%
Incremental cost per additional mutation identified		\$9,762

The current rate of surveillance is a key uncertainty; the base-case (which assumes that 100% of untested family members participate in surveillance, and following genetic testing mutation negative family members drop out of surveillance) is likely to overestimate the cost-savings and underestimate the clinical benefits of testing. Conversely, the alternative scenario (that assumes no untested family members participate in active surveillance, but tested mutation positive family members take up surveillance) is likely to overestimate both the additional cost of testing and the clinical benefit.

The incremental cost-effectiveness ratios across varying mixed proportions of these scenarios is presented in Table 3, with dominant incremental cost-effectiveness ratios (ICERs) (less costly and more effective) for index and familial testing occurring at rates of familial surveillance in untested family members above 50% to less than 98%.

Table 3 Lynch Syndrome ICERs for genetic testing for index cases and family members of index cases, with varying levels of adherence-to recommended familial surveillance (weighted analyses of base case and alternative scenarios; where % of base case represents % adherence to surveillance in a non-tested familial population. (Discounted)

Scenario weighting	Inc. costs	Inc. QALYs	ICER
100% base case; 0% alternative scenario	-\$10,914	-0.0046	\$2,393,152 saved per QALY lost
99% base case; 1% alternative scenario	-\$10,694	-0.0028	\$3,813,492 saved per QALY lost
98% base case; 2% alternative scenario	-\$10,473	-0.0010	\$9,997,023 saved per QALY lost
97% base case; 3% alternative scenario	-\$10,252	0.0007	Dominant (cost saving and QALY gained)
90% base case; 10% alternative scenario	-\$8,706	0.0130	Dominant (cost saving and QALY gained)
80% base case; 20% alternative scenario	-\$6,497	0.0306	Dominant (cost saving and QALY gained)
70% base case; 30% alternative scenario	-\$4,288	0.0481	Dominant (cost saving and QALY gained)
60% base case; 40% alternative scenario	-\$2,079	0.0657	Dominant (cost saving and QALY gained)
50% base case; 50% alternative scenario	\$130	0.0833	\$1,559 per additional QALY gained
40% base case; 60% alternative scenario	\$2,339	0.1008	\$23,194 per additional QALY gained
30% base case; 70% alternative scenario	\$4,548	0.1184	\$38,409 per additional QALY gained
20% base case; 80% alternative scenario	\$6,756	0.1360	\$49,692 per additional QALY gained
10% base case; 90% alternative scenario	\$8,965	0.1535	\$58,394 per additional QALY gained
0% base case; 100% alternative scenario	\$11,174	0.1711	\$65,309 per additional QALY gained

ICER = incremental cost effectiveness ratio; QALY = Quality-adjusted life-year

Likewise, for patients suspected of familial polyposis, genetic testing will not change clinical management or outcomes, thus the economic analysis of cost per mutation identified is the only relevant analysis. Subsequent to mutation identification, familial testing is expected to change surveillance rates in family members of index cases. Given the gravity of the clinical diagnosis, the base case analysis in FP also assumes untested family members will participate in surveillance. The results of the cost-effectiveness analysis for index and familial testing for FP are shown in Table 4. There is insufficient data on long-term survival outcomes and quality of life in FP to populate a test vs no test cost-utility analysis.

Table 4 Familial Polyposis: Cost-effectiveness of genetic testing for index cases + family members of index cases vs no testing, (base case scenario with full surveillance, discounted)

	Genetic testing	No testing	Increment	Incremental cost/effect
Index case				
Costs	\$1,596	\$0	\$1,596	
Mutations identified	28%	0%	28%	\$5,691 per mutation identified
+ Family members				
Cost	\$111,844	\$137,948	-\$26,104	-
Colorectal cancer	0.0552	0.0537	0.0015	\$17,241,886 cost saving per additional CRC case

CRC = Colorectal cancer

In the FP and family population, when the assumption that family members adhere to recommended surveillance is reversed, i.e. no surveillance is undertaken in untested family, but genetic testing results in surveillance in positive carriers, the ICER becomes dominant (both cost saving and with health benefit). As with LS, a weighted analysis with mixed

compliance patterns is likely to show that genetic testing becomes dominant even with small rates of non-compliance in untested family members.

With the exception of the assumption around surveillance compliance rates, the sensitivity analyses did not identify other variables that significantly changed the conclusions of the base case analysis in either LS or FP.

13. Financial/budgetary impacts

The proposed genetic testing for inheritable mutations predisposing people to colorectal and endometrial cancer, and the associated pre-test and post-test counselling, are estimated to have direct costs to the MBS of \$3.3 million to \$3.5 million per year, over the years 2019-2023 (see Table 5).

Table 5 Total estimated cost to the MBS for genetic testing for inheritable mutations predisposing people to colorectal and endometrial cancer, and associated genetic counselling, 2019-2023

Service	MBS Cost	2019	2020	2021	2022	2023
Diagnostic tests	\$1,118	\$1,928,347	\$1,959,768	\$1,990,988	\$2,022,154	\$2,053,227
Predictive tests	\$340	\$380,564	\$386,765	\$392,927	\$399,077	\$405,210
Genetic counselling	\$337	\$957,450	\$973,051	\$988,552	\$1,004,026	\$1,019,455
Total net cost to MBS of genetic testing and counselling		\$3,266,361	\$3,319,585	\$3,372,468	\$3,425,258	\$3,477,892

MBS = Medicare Benefits Schedule

However these estimates do not consider the anticipated downstream costs or savings associated with surveillance, prophylactic surgeries or cancer treatments. A significant proportion of these downstream services are currently funded by MBS.

Factors which will vary the usage of downstream services include; for example, whether or not genetic testing is performed to diagnose at-risk relatives before the occurrence of malignancy; if so the test may result in increased costs associated with surveillance but reduced cancer treatment costs. An important benefit is to avoid unnecessary surveillance and prophylactic surgeries in the mutation-negative family members; this will result in cost savings by avoiding unnecessary colonoscopies and surgeries. Overall a mix of these clinical scenarios is expected to occur in practice, but given intensive surveillance is recommended, further downstream MBS cost savings are anticipated.

While the expected reduction in surveillance in family members is a relatively direct effect of testing, there are no data available to accurately estimate the number of family members who currently participate in surveillance, thus the magnitude of these cost-offsets is highly uncertain. Furthermore, the likely reduction in associated MBS surveillance costs occurs many years into the future and will be less significant in the immediate budget estimates 2019 – 2023, but continue to accrue significantly beyond these years.

Future MBS cost-offsets associated with potential reductions in cancer treatment costs may also be considered an indirect financial impact. These too are uncertain as they will also depend on the extent to which family members currently participate in surveillance, and may also occur beyond 2023.

Key issues from ESC for MSAC

ESC KEY ISSUES	ESC ADVICE
Complex CUC covers 6 diseases; most data for Lynch Syndrome (LS) and familial adenomatous polyposis (FAP). NB EuroGen CUC has 2 for LS, 1 for FAP	Note population, clinical, genetic heterogeneity between and within diseases, some relatively uncommon with limited data e.g. HMPS. Clinical utility data mainly on Lynch Syndrome (LS).
Comparator clinical pathway is no testing, whereas test comparator is Sanger/MLPA/array	Note genetic testing recommended by EviQ. Note the CUC economics and financials suggests that widespread panel-based testing for hereditary colorectal cancer (CRC) only began in 2012 (mid 2016 in Australia). Limited data in relation to the benefit of incremental panel testing over current/EviQ practice.
Panels may include both highly penetrant as well as moderately penetrant genes	Panel-based testing likely to identify more mutations, may increase the complexity of interpretation of results.
Uncertainty re discordant results on management	Would a negative genetic test in someone with 100/1000s of polyps change clinical practice?
Open item definition makes results of economic evaluation depend on gene combinations included in the panel	The proposed item descriptor can lead to a number of gene combinations being tested. The economic model reflects one particular set with the number of genes greater than the minimum included in the item descriptor. Some standardisation might be useful, e.g. by requiring that the test panel includes at least <i>MLH1</i> , <i>MSH2</i> , <i>MSH6</i> , <i>PMS2</i> , <i>EPCAM</i> , <i>APC</i> and <i>MUTYH</i> (as assumed in the economic evaluation).
Two separate models make it difficult to assess overall economic characteristics of the proposed item	This is especially in the context of an open definition of gene panel for testing. It was not clear if integrating LS and adenomatous polyposis syndromes into one model was feasible, and whether this could overcome structural limitations of the evaluation.
Definition of the comparator	Is no testing an appropriate comparator? Economic literature (in particular UK's Snowsill 2015, also review by Grosse 2015) suggests that genetic testing might be cost-effective vs no testing, however it is less clear if it would be cost-effective vs other viable comparators (MSI and IHC tests as current practice in LS).
Adherence to surveillance strategies: is it sufficiently well captured in the model?	In the model this is done by weighting the results of two extreme cases. It was not clear if this adequately represented current/new practice. Secondly, do at-risk patients actually follow their scheduled appointments? It would be helpful if the model approach in this area could be validated
Model uncertainty	Whether we accept the heterogeneity of sources of input data and evidence, and agree with the structural assumptions

ESC discussion

ESC noted that this was a CUC expedited application that had bypassed PASC. The CUC served as the clinical evaluation of genetic testing for heritable mutations for colorectal and endometrial cancer. ESC noted that this was the first time that it had looked at such a submission since the pilot study in breast and ovarian cancer.

ESC noted that submission requests two MBS item numbers for genetic testing. One item is for multigene testing for mutations or deletions in three or more genes in individuals (the potential proband) with inherited syndromes associated with increased predisposition to colorectal and endometrial cancer. The genes in question are *APC*, *MLH1*, *MSH2*, *MSH6*, *PMS2* or *MUTYH* with or without testing of *SMAD4*, *BMPRI1A*, *STK11*, *GREM1* and *EPCAM*. The other item is for cascade testing of the proband's family members.

ESC noted that the syndromes in question included Lynch syndrome, FAP, MAP, JPS, PJS and HMPS. ESC noted that the bulk of the evidence presented in the submission was for Lynch syndrome and FAP.

ESC noted that the submission covered a large number of genes and conditions and so information about some genes and conditions was very limited. ESC queried whether this may have been to the detriment of some of the conditions. ESC noted that there are separate European CUCs for Lynch syndrome, FAP and MAP.

ESC noted that the lifetime risk of cancer varied according to condition and, among people with Lynch syndrome, according to the type of mutation they carry. ESC noted that the probability of detecting a mutation or deletion among individuals who met the clinical criteria for a condition also varied according to the type of condition. In Lynch syndrome the probability of detecting a mutation was 33–55%, while in FAP it was 30–93% depending on the number of polyps reported for a patient.

ESC noted that the CUC nominated 'star performer' genes (i.e. actionable genes with the strongest clinical utility) for three of the conditions:

- *MLH1*, *MSH2*, *MSH6* and *PMS2* for Lynch syndrome;
- *APC* for FAP; and
- *MUTYH* for MAP.

ESC noted that the CUC identified additional actionable genes for four of the conditions:

- *EPCAM* (for deletions associated with epigenetic silencing of *MSH2*) for Lynch syndrome;
- *SMAD4*, *BMPRI1A* and *STK11* for JPS;
- *SMAD4*, *BMPRI1A* and *STK11* for PJS; and
- *GREM1* for HMPS.

ESC noted the analytical reference standard proposed in the application was Sanger sequencing. ESC noted the CUC claimed that there were numerous studies in which established gene panels have been shown to have equivalent analytical sensitivity and specificity to Sanger sequencing.

ESC noted that the comparator for multigene testing in people with Lynch syndrome or FAP was no genetic testing. ESC considered that this may reflect old guidelines and that a more appropriate comparator would be immunohistochemistry (IHC) and microsatellite instability (MSI) testing.

ESC noted that no comparative safety evidence had been provided. ESC considered that as genetic testing is performed on a blood sample it is assumed to have a low risk of harm.

ESC considered that there was limited evidence that genetic testing improves outcomes for the proband and suggested that any benefit to the proband is likely to be smaller than that which accrues to family members. However, ESC noted that there was some evidence from observational studies that there may be some validity in genetic testing for the proband. In one study which followed 252 people with Lynch syndrome who were mutation positive, the subjects who underwent active surveillance with regular colonoscopies developed fewer colorectal cancers than those who declined surveillance (Jarvinen HJ et al 2000). In another study of 609 people with Lynch syndrome, rates of cancer were higher in the mutation positive group than in the mutation negative group but mortality rates were similar (Jarvinen HJ et al 2009). However, the mutation positive subjects were offered active surveillance which suggests that ongoing surveillance in mutation positive patients leads to earlier detection of cancer and prevents death.

In contrast, ESC noted that among 419 patients with PJS who were followed over time, there was no difference in cancer rates in those who had an *STK11* mutation compared with those who did not (Hearle N et al 2006). ESC noted that the applicant had argued that this may have been because PCR analysis at the time of the study was less sensitive.

ESC noted that the clinical claim for genetic testing in family members is that if they test negative, they will no longer need to undergo regular surveillance for cancer, such as colonoscopies. Family members who test positive will continue to undergo surveillance and some women may choose to undergo preventive hysterectomy or salpingo-oophorectomy.

ESC noted that the evidence to support the clinical effectiveness of cascade testing was limited, but the CUC claimed that the ratio of clinical events in mutation positive family members to mutation negative family members was the same as the ratio of clinical events in mutation positive family member to the general population.

ESC noted that an economic model had been provided for Lynch syndrome and another for FAP and MAP, but not for the other syndromes. ESC queried whether it was possible to combine the information about Lynch syndrome, FAP and MAP into a single model.

ESC considered that the economic modelling was of limited value because the comparator used was no genetic testing, rather than IHC and MSI. ESC suggested that the modelling be redone with an appropriate comparator.

While ESC was concerned about the comparator, it considered that the structure, health states, outcomes and sensitivity analyses included in the two models were largely reasonable.

ESC queried some of the assumptions in the models including that:

- testing has no implications for clinical management of index cases which means that all the utility accrues to family members, not the proband. ESC suggested that some of the literature indicated genetic testing may have some utility in people with early colorectal cancer;
- in the absence of genetic testing, there would be full adherence to surveillance in family members of the proband. ESC acknowledged that an alternative scenario had been provided in which none of the family members underwent surveillance, and a range of ICERs varied according to different scenario weightings. ESC was not convinced this was an appropriate approach. ESC considered that mixing together the results from two extreme scenarios was not an adequate substitute for undertaking sensitivity analysis; and

- increased survival and quality of life is not modelled in the FAP and MAP model.

ESC also noted that the lack of clarity about which, and how many, genes should be included in the test panels introduced further uncertainty into the economic model.

ESC noted that, because the model assumed that genetic testing did not change management for the proband, the ICER for the population of affected individuals reflects the incremental cost per mutation identified, not the incremental cost per quality adjusted life year (QALY).

ESC noted that, while a review of economic literature had been undertaken, the identified papers had been inadequately discussed. ESC noted that one of the papers was a review of cost-effectiveness analyses (Grosse SD 2015). ESC noted that, unlike the submission, some of the studies included in the Grosse review were able to generate incremental costs per QALY for genetic testing of index patients with colorectal cancer and a clinical suspicion of Lynch syndrome.

ESC considered that the impact of the choice of comparator used in the economic modelling had not been adequately explored. ESC particularly noted a UK study that looked at the cost-effectiveness of different strategies to identify Lynch syndrome in individuals with early-onset colorectal cancer (Snowsill T et al 2015). ESC noted that this paper suggested that, if an IHC four-panel test followed by mutation testing for abnormal IHC results was compared with no genetic testing, the ICER was ~£25,000 per QALY. However, if the comparison was between direct mutation testing and no genetic testing, the ICER was ~£82,000 per QALY. ESC considered that this provided further evidence that the modelling should be redone with an appropriate comparator.

ESC noted that there was a slight increase in the number of colorectal cancers seen among the family members of probands because family members who tested negative stopped surveillance but remained at risk of developing cancer at the general population rate.

ESC noted advice from the Department that the provision of genetic counselling is considered to be part of a specialist's standard of care, but that it cannot be claimed as an MBS service. ESC advised that using the fee for MBS item 132 (professional attendance by a consultant physician) as a proxy for genetic counselling in both the economic model and the financial estimates was appropriate in the context of the economic and financial modelling.

ESC noted that fees currently charged by different Australian laboratories for mutation testing in probands and family members vary greatly (~\$200–1500). However, ESC suggested that without further information on the methods (next-generation sequencing, MSI, multiplex ligation-dependent probe amplification (MLPA), microarray, etc) and procedures (confirmatory testing, etc) each laboratory used it was difficult to use these fees as a guide for the MBS fee.

ESC noted that fees currently charged by different Australian laboratories for mutation testing in probands and family members vary greatly (~\$200–\$1500). ESC noted that interpretation of the results from multigene testing is likely to be more complex and may require a longer than usual period of pathologist time. However, ESC suggested that without further information on the methods (next-generation sequencing, MSI, MLPA, microarray, etc) and procedures (confirmatory testing, etc) each laboratory used, and the relative complexity of interpretation, it was difficult to use these fees as a guide for the MBS fee.

ESC noted that the suggested MBS fee was aligned with MBS items 73296 (\$1200) and 73297 (\$400) which are for germline mutation testing of *BRCA1* and *BRCA2* genes and one or more other genes in probands and their relatives, respectively.

ESC advised that the key genes to be characterised by the testing panel need to be clearly identified in the item descriptor. ESC noted that the proposed MBS item descriptor did not indicate whether all or some of the identified genes needed to be characterised. ESC noted the applicant had proposed that testing of the star performer genes could be conducted with or without the additional actionable genes, and as such the additional actionable genes have no influence upon determining eligibility for the MBS-subsidised genetic testing (despite being the only genes identified as being clinically useful for JPS, PJS and HMPS).

ESC noted that the item descriptor for cascade testing had been amended so that it is similar to MBS item 73297 for cascade testing of the relatives of probands with breast or ovarian cancer and an identified pathological mutation.

14. Other significant factors

Nil

15. Applicant's comments on MSAC's Public Summary Document

No errors of fact have been noted in the document, however, the College is most concerned about the process that this application was reviewed under. The College submitted an application for 1504, which was requested to be "converted" to a Clinical Utility Card (CUC) when triaged by the Department. Unlike a similar application (1534 Familial hypercholesterolaemia), this CUC was an expedited application that did not undergo scrutiny by the PASC, which, in hindsight, may have impeded the process.

The College agrees with MSAC that this is a complex application. The College is, however, concerned and requests clarification about whether MSAC is requesting a revision of the existing CUC into three separate applications or whether we could work with the Department to revise the wording of the proposed item descriptor into three distinct item numbers (for proband and cascade screening) for LS/nonpolyposis (MLH1, MSH2, MSH6, PMS2, EPCAM), familial adenomatous polyposis (APC, MUTYH), and familial non-adenomatous polyposis (SMAD4, BMPR1A, STK11, GREM1) in addition to providing cost and utilisation data. The College would prefer the latter.

The College would also like it noted that a revised CUC was developed in response to feedback received from the Predisposition Genetic Testing Working Group. However, the revised CUC could not be considered by the ESC. As this application was only the second CUC considered by ESC, greater flexibility in this respect may have been ultimately more efficient.

16. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)