MJA
The Medical Journal of Australia

Supporting Information

Supplementary information on methods and analyses; supplementary analyses

This appendix was part of the submitted manuscript and has been peer reviewed. It is posted as supplied by the authors.

Appendix to: Kang YJ, Killen J, Caruana M, et al. The predicted impact and cost-effectiveness of systematic testing of people with incident colorectal cancer for Lynch syndrome. *Med J Aust* 2019; doi: 10.5694/mja2.50356.

The predicted impact and cost-effectiveness of systematic testing of people with incident colorectal cancer for Lynch syndrome: supporting information

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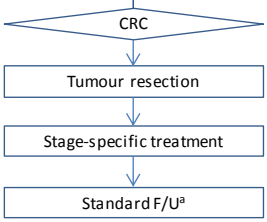
1. Policy1–Lynch

We have developed a range of modelling tools for the evaluation of cancer screening and surveillance strategies. *POLICY1*, implemented in C++, is an individual-based (ie, microsimulation) discrete event framework for simulating different cancers and various screening and surveillance strategies (http://www.policy1.org). It was developed to serve as a common simulation platform for different cancer types and is linked to a range of calibration, one-way and probabilistic sensitivity analysis (PSA) tools. The platform can model several different cancers developing in an individual simultaneously (as required for Lynch syndrome [LS]).

We used a microsimulation model (*Policy1–Lynch*) to simulate the impact of various LS testing strategies in people with colorectal cancer (CRC). We explicitly modelled the cost of testing all patients diagnosed with CRC in 2017, with detailed modelling of patients identified as LS carriers (probands) and their at-risk relatives throughout their lifetimes, to 100 years of age. For people with confirmed LS, we modelled ongoing colonoscopic surveillance for CRC detection. The current version of *Policy 1–Lynch* simulates CRC in carriers and non-carriers of LS, and comprises four components, including a model of testing for LS in patients with incident CRC (identifying probands), a model of testing for LS in family members (predictive genetic testing), a model of prophylaxis and surveillance (prophylactic surgery, colonoscopic surveillance), and a model of invasive cancer (cancer treatment and survival). The simulation was performed for one million people with CRC and LS in each 5-year age group and their at-risk relatives.

2. Testing for Lynch syndrome: clinical management flow charts

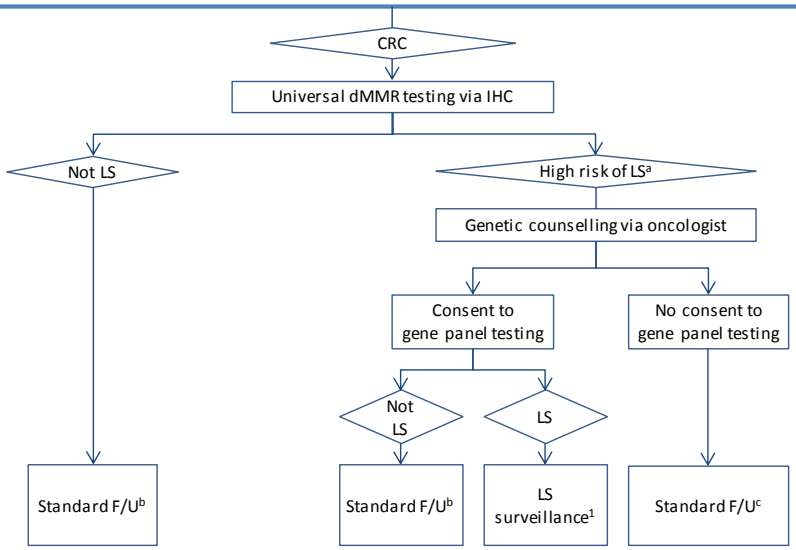
Scenario 1: (theoretical) no CRC tumour testing (i.e. comparator)



CRC = colorectal cancer.

a. We do not explicitly model standard care after cancer treatment; however, stage- and site-specific cancer treatment costs include the cost of initial treatment, the cost of follow-up appointments, blood tests and imaging, treatment for relapsed disease, and palliative care.

Scenario 2: IHC tumour testing followed by diagnostic gene panel testing



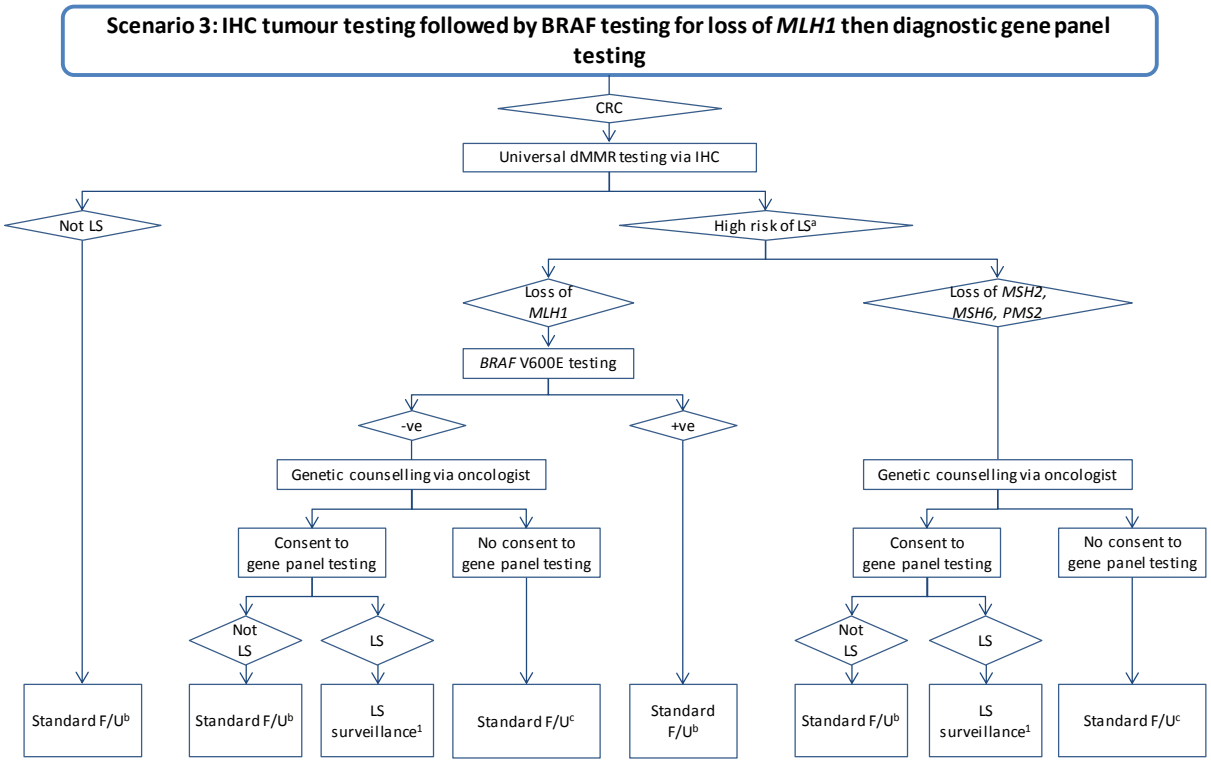
CRC = colorectal cancer; dMMR = DNA mismatch repair deficiency; F/U = follow-up; IHC = immunohistochemistry testing; LS = Lynch syndrome.

a. High risk of LS includes abnormal IHC results (absence of staining for MLH1/MSH2/MSH6/PMS2).

b. We do not explicitly model standard care after cancer treatment; however, stage- and site-specific cancer treatment costs include the cost of initial treatment, the cost of follow-up appointments, blood tests and imaging, treatment for relapsed disease, and palliative care.

c. There will be a small proportion of people whose tumour specimen shows dMMR and with a family history suggesting LS, but who do not consent to genetic testing. In theory, these individuals will be managed with LS surveillance, but we made the simple assumption that they will not receive LS surveillance.

1. See detailed clinical management flow chart in "Colonoscopic surveillance and CRC risk reducing surgery in confirmed LS carriers"



CRC = colorectal cancer; dMMR = DNA mismatch repair deficiency; F/U = follow-up; IHC = immunohistochemistry testing; LS = Lynch syndrome.

a. High risk of LS includes abnormal IHC results (absence of staining for MLH1/MSH2/MSH6/PMS2).

b. We do not explicitly model standard care after cancer treatment; however, stage- and site-specific cancer treatment costs include the cost of initial treatment, the cost of follow-up appointments, blood tests and imaging, treatment for relapsed disease, and palliative care.

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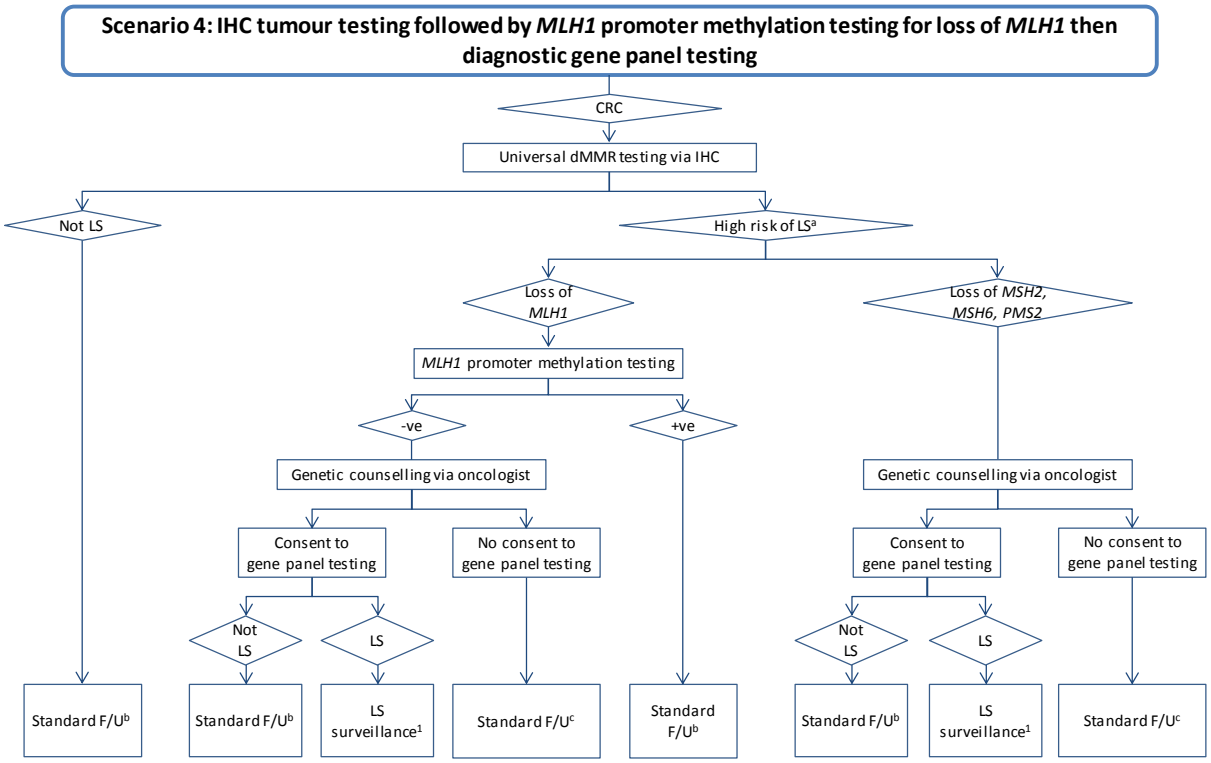

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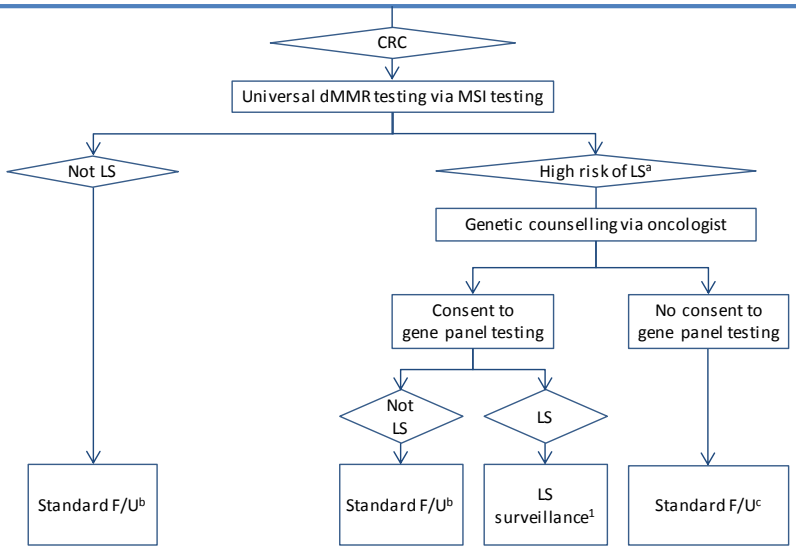
Scenario 5: MSI tumour testing followed by diagnostic gene panel testing



CRC = colorectal cancer; dMMR = DNA mismatch repair deficiency; F/U = follow-up; LS = Lynch syndrome; MSI = microsatellite instability.

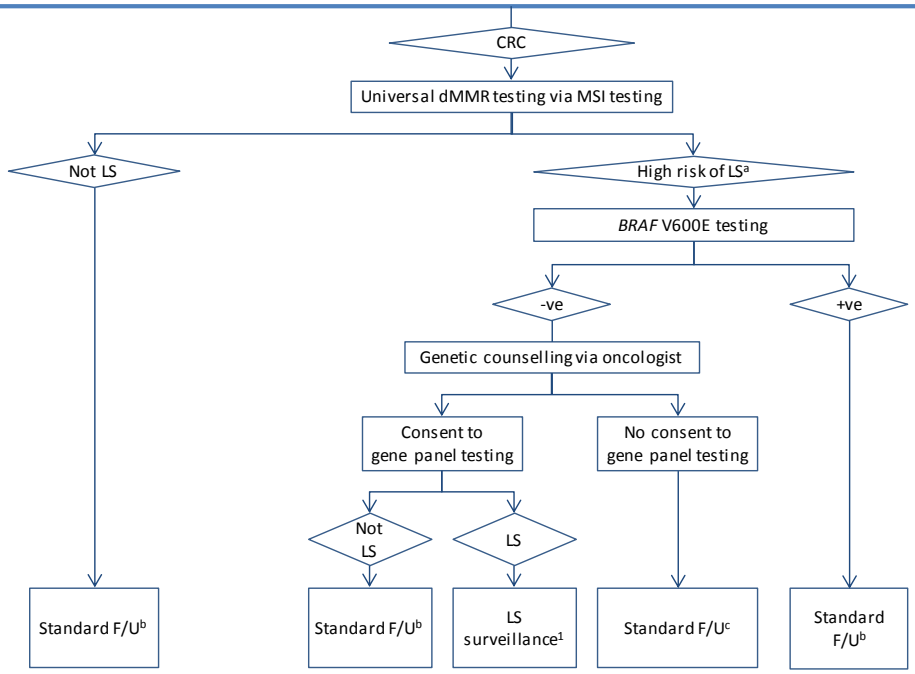
a. High risk of LS includes high level of MSI.

b. We do not explicitly model standard care after cancer treatment; however, stage- and site-specific cancer treatment costs include the cost of initial treatment, the cost of follow-up appointments, blood tests and imaging, treatment for relapsed disease, and palliative care.

c. There will be a small proportion of people whose tumour specimen shows dMMR and with a family history suggesting LS, but who do not consent to genetic testing. In theory, these individuals will be managed with LS surveillance, but we made the simple assumption that they will not receive LS surveillance.

1. See detailed clinical management flow chart in "Colonoscopic surveillance and CRC risk reducing surgery in confirmed LS carriers"

Scenario 6: MSI tumour testing followed by *BRAF* testing then diagnostic gene panel testing



CRC = colorectal cancer; dMMR = DNA mismatch repair deficiency; F/U = follow-up; LS = Lynch syndrome; MSI = microsatellite instability.

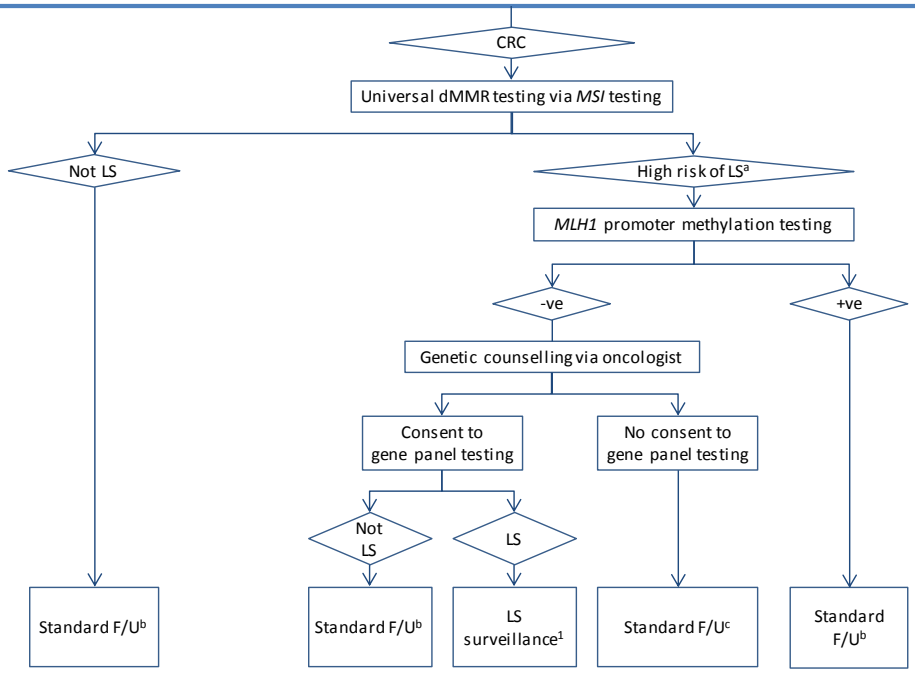
a. High risk of LS includes high level of MSI.

b. We do not explicitly model standard care after cancer treatment; however, stage- and site-specific cancer treatment costs include the cost of initial treatment, the cost of follow-up appointments, blood tests and imaging, treatment for relapsed disease, and palliative care.

c. There will be a small proportion of people whose tumour specimen shows dMMR and with a family history suggesting LS, but who do not consent to genetic testing. In theory, these individuals will be managed with LS surveillance, but we made the simple assumption that they will not receive LS surveillance.

1. See detailed clinical management flow chart in "Colonoscopic surveillance and CRC risk reducing surgery in confirmed LS carriers"

Scenario 7: MSI tumour testing followed by *MLH1* promoter hyper-methylation testing then diagnostic gene panel testing



CRC = colorectal cancer; dMMR = DNA mismatch repair deficiency; F/U = follow-up; LS = Lynch syndrome; MSI = microsatellite instability.

a. High risk of LS includes high level of MSI.

b. We do not explicitly model standard care after cancer treatment; however, stage- and site-specific cancer treatment costs include the cost of initial treatment, the cost of follow-up appointments, blood tests and imaging, treatment for relapsed disease, and palliative care.

c. There will be a small proportion of people whose tumour specimen shows dMMR and with a family history suggesting LS, but who do not consent to genetic testing. In theory, these individuals will be managed with LS surveillance, but we made the simple assumption that they will not receive LS surveillance.

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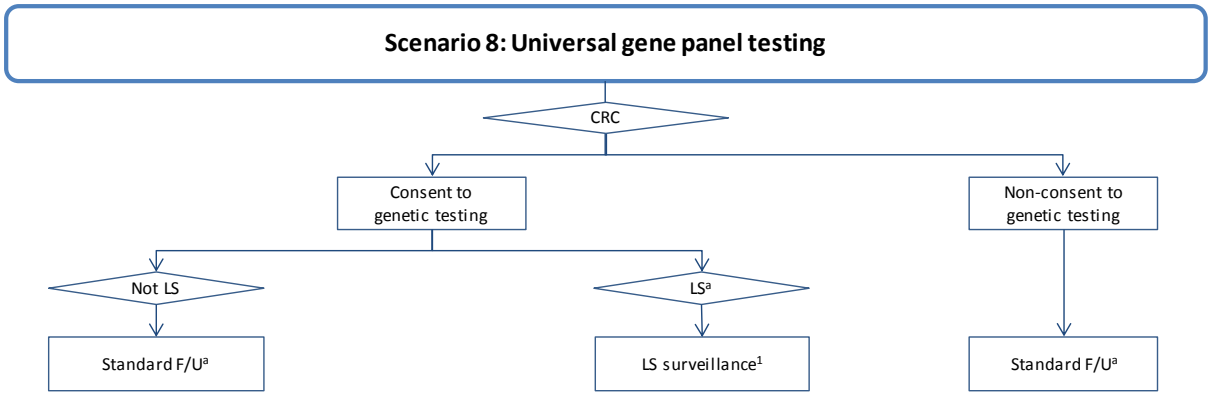

CRC = colorectal cancer; F/U = follow-up; LS = Lynch syndrome.

a. We do not explicitly model standard care after cancer treatment; however, stage- and site-specific cancer treatment costs include the cost of initial treatment, the cost of follow-up appointments, blood tests and imaging, treatment for relapsed disease, and palliative care.

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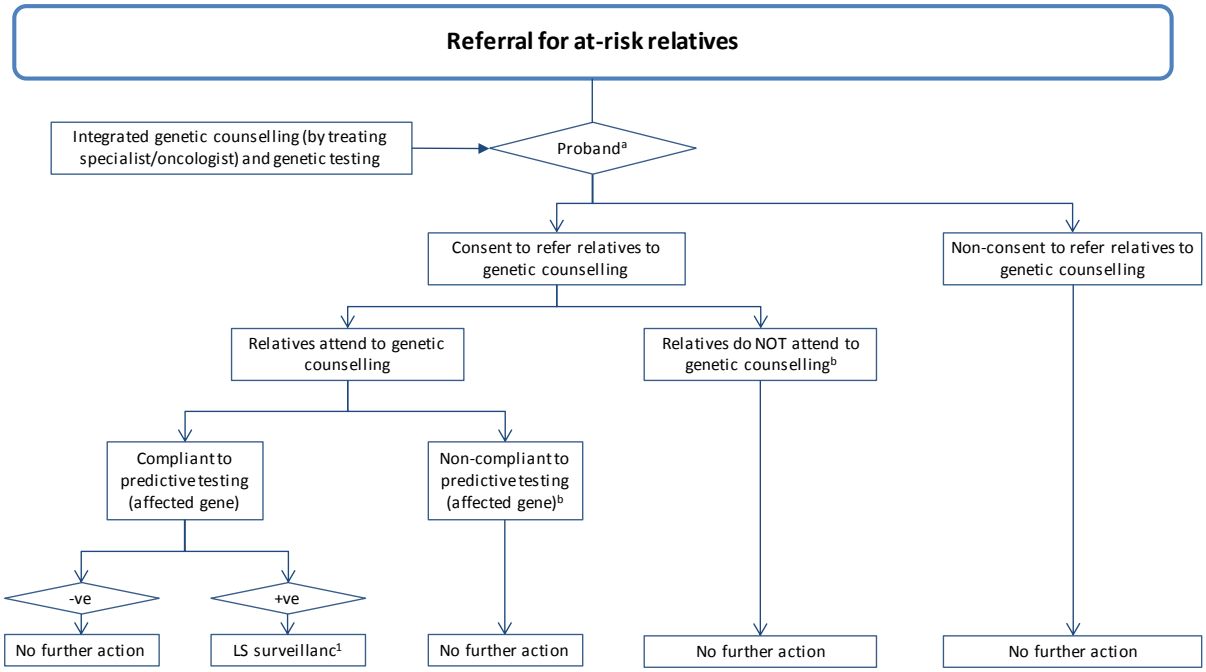
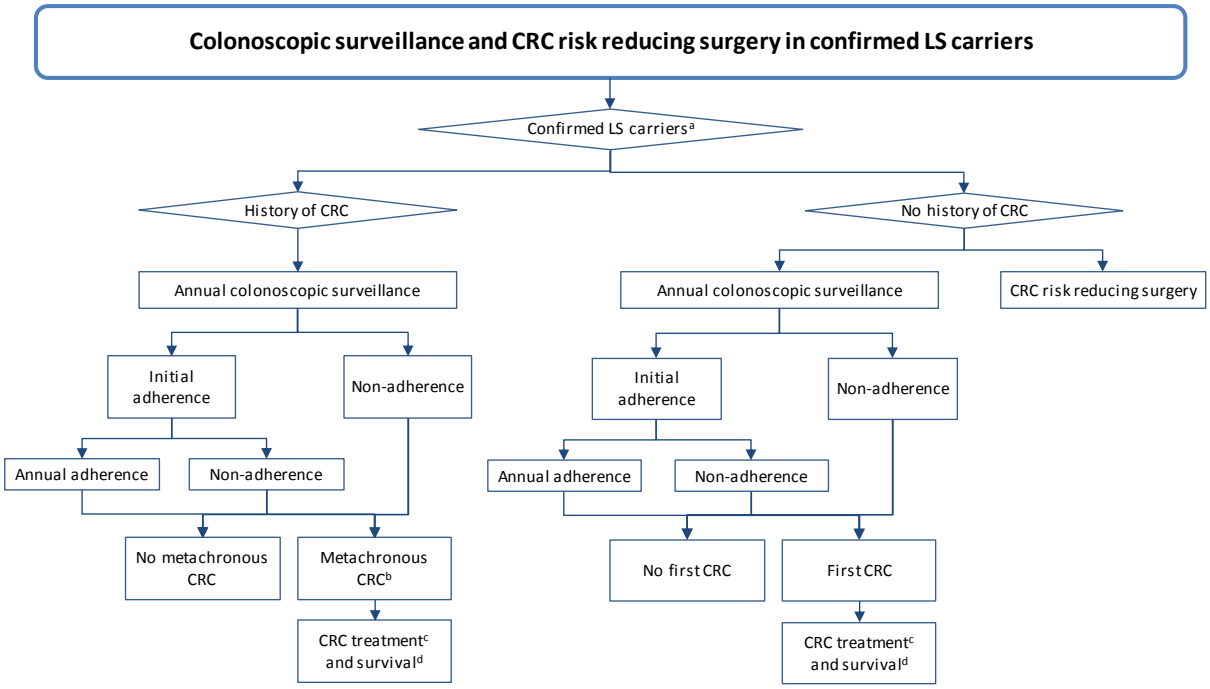


LS = Lynch syndrome.

a. We assume genetic counselling for probands (patients with incident cancer and LS confirmed by diagnostic germline genetic testing) is performed by the treating clinician/specialist as part of a mainstreaming process.

b. We assume relatives without confirmed LS will not receive LS surveillance.

1. See detailed clinical management flow chart in "Colonoscopic surveillance and CRC risk reducing surgery in confirmed LS carriers"



CRC = colorectal cancer; LS = Lynch syndrome

a. Confirmed LS carriers include both probands and relatives.
b. Metachronous CRC site depends on the previous CRC surgery type.
c. Surgical options for colon cancer include segmental resection and colectomy. Site of metachronous CRC depends on previous cancer site and surgery. Surgical options for rectal cancer include anterior resection and proctocolectomy. Site of metachronous cancer depends on previous cancer site and surgery.
d. We used stage-specific CRC survival at 5 years in Australia. In our baseline assumption, the 5-year survival from stage I/II CRC in LS carriers is 43% higher than in non-LS-CRC cases at the same stage disease, and the 5-year survival for stage III/IV CRC in LS carriers is the same as in non-LS-CRC cases (the effect of this assumption was assessed in sensitivity analysis). The population life tables were used for calculating other cause of death.

3. Overview of model specification and structural assumptions

Table 1. Summary of the model specification and structural assumptions

Specification	Key assumption
Model type	Microsimulation model

Target population	Proband (index cancer cases identified as LS carriers)
	• Person diagnosed with incident colorectal cancer (CRC) in 2017
	  ○ All ages
	  ○ Maximum age for testing: < 50, < 60 and < 70 years at diagnosis
	Relatives
	• 1st degree relatives: children and siblings of proband
	• 2nd degree relatives: LS sibling's children

Intervention	Proband • Universal dMMR tumour testing (IHC or molecular MSI test) with/without reflex testing (*BRAF* V600E mutation or *MLH1* promoter hypermethylation test), then diagnostic germline gene panel testing to confirm LS; or • Universal germline gene panel testing (genetic counselling is performed by a treating clinician/oncologist) Relatives • Genetic counselling, then predictive genetic testing for the targeted gene (cascade testing)
Comparator	No LS testing. Although dMMR tumour testing in people with CRC can be performed in Australia, in the absence of a uniform national LS testing policy and substantial variation in the current availability and practice of dMMR tumour testing, we examined the impact of (theoretical) no testing as comparator for assessing the cost-effectiveness of dMMR testing.[1]
Outcomes	• Total costs, life-years saved (LYS), costs per LYS ($/LYS) • CRC cases and deaths, CRC deaths averted • Number of colonoscopies • Number of colonoscopies to avert one CRC death
Time horizon	• Lifetime: We modelled LS carriers whose CRC was diagnosed in 2017 in Australia (probands) and their at-risk relatives throughout their lifetimes, to 100 years of age. The simulation was performed for 1 million people with CRC and LS in each 5-year age group and their at-risk relatives, and the results were aggregated for the cohort of LS carriers identified in 2017.
Perspective	Health care provider perspective in Australia (ie, Medicare costs)
Discount rate	A discount rate of 5% was applied to both costs and effects
Currency	All costs were presented in 2017 Australian dollars
Willingness to pay threshold	$30 000–$50 000/LYS, consistent with prior Medical Services Advisory Committee evaluation of the National Cervical Screening Program in Australia[2] and vaccine applications to the Pharmaceutical Benefits Advisory Committee (PBAC) recommending a lower cost-effectiveness threshold for preventive programs.[3]
Natural history of CRC	• CRC development was modelled as single transition (well to invasive CRC) • First CRC incidence in LS carriers: sex-specific cumulative risk of CRC to age 80 years with and without colonoscopic surveillance, averaged across four MMR genes mutated[4,5] • CRC incidence in general population: observed sex- and age-specific incidence in Australia, 2014 (the most recent available data)[6] • Up to two CRCs during lifetime (up to one metachronous CRC) • CRC stage at diagnosis depends only on whether the person was undergoing LS colonoscopic surveillance (down-staging)[7,8] • The site of incident CRC was dependent on LS status and the site of metachronous CRC was dependent on previous surgery type[7,8] • Impact of colonoscopic surveillance on CRC in LS carriers

Specification	Key assumption
	○ Baseline assumption: down staging and reduction in CRC incidence (70% reduction in the incidence of the first CRC with annual colonoscopic surveillance, 61% reduction in the incidence of the first CRC with 2-yearly colonoscopic surveillance,[4,7,8] and 47% reduction in the incidence of metachronous CRC with annual/2-yearly colonoscopic surveillance[7-9]) ○ Alternative assumption (sensitivity analysis): down-staging only • Comorbid disease states were not considered • Calibration/validation for the natural history model was not performed as we used published rates directly • Uncertainty analysis and one-way sensitivity analysis were performed on key assumptions on the natural history model
Testing and triage to identify probands	• All patients diagnosed with incident CRC in Australia in 2017 are tested for LS by universal dMMR tumour testing or universal germline gene panel testing ○ The proportion of patients with CRC who are men is 55%, as in Australia in 2014.[6] ○ The prevalence of LS in people with incident CRC at all ages is 2.8%,[10] 55% of whom are male LS carriers[6] • Testing uptake rates by people with incident CRC ○ dMMR tumour test uptake is 100%, assuming all CRC specimens are sent to pathology laboratories if universal testing takes place ○ Genetic counselling is performed by the treating clinician/specialist as part of a mainstreaming process, so adherence was not considered ○ The diagnostic germline genetic testing uptake by people with incident CRC is assumed to be 90% in all testing strategies, assuming they are provided with appropriate information/education on the benefits of testing • Test characteristics ○ MMR IHC: The sensitivity and specificity of MMR IHC test is based on loss of expression of one or more of the four MMR proteins;[8] sensitivity, 0.962; specificity, 0.884[8] ○ MSI-high: We assumed MSI-high as test positive;[8] sensitivity, 0.913;[8] specificity, 0.837[8] ○ *BRAF* V600E: sensitivity, 0.96;[11] specificity, 0.76[11] ○ *MLH1* promoter hypermethylation testing: sensitivity, 0.94;[11] specificity, 0.75[11] • Gene panel testing ○ For modelling simplicity, we assumed the sensitivity and the specificity of germline gene panel testing is 100%, based on the evidence that the sensitivity and the specificity of germline gene panel testing for LS is 99.4%[12,13] ○ Variants of uncertain significance are not informative and were therefore not considered[14] ○ The impact of an incidental diagnosis (eg, non-LS hereditary cancers) resulting from the universal germline gene panel testing was not considered • We did not explicitly model colonoscopy test characteristics, as the CRC incidence reduction associated with regular colonoscopic surveillance already captured the sensitivity and specificity of colonoscopy as part of the overall effectiveness of surveillance. • Calibration/validation on screening/cascade testing adherence was not performed as we used published rates directly
Targeted predictive cascade testing for at-risk family members	• Proband referral for at-risk family members ○ It was assumed that 90% of probands inform their relatives of risk and suggest cascade testing ○ Of the relatives referred to genetic services, 78% attend genetic counselling, of whom 77% accept genetic testing[8] ○ Cascade testing is assumed to take place within the first year of a proband's CRC diagnosis • At-risk relatives for each proband ○ The proportion of relatives with LS is 44%[8] ○ Relatives do not have a prior CRC diagnosis

Specification	Key assumption
	○ A mean six relatives (siblings, children, LS siblings' children) per proband are eligible for LS cascade testing and 1.42 of them are identified as LS carriers after predictive germline genetic testing ○ We assumed an equal number of proband's siblings, proband's children, and children of siblings with confirmed LS among the proband's relatives ○ Number of children per proband and the age distribution of proband's children were based on Australian data[15] • Test characteristics: We assumed the sensitivity and the specificity of targeted genetic testing for relatives is 100% • Sensitivity analysis was performed on the average number of relatives eligible for LS cascade testing
Surveillance/ prophylaxis	• Colonoscopic surveillance of confirmed LS carriers ○ Only carriers with LS confirmed by germline genetic testing are referred for annual colonoscopic surveillance, and surveillance start and end age are in accordance with clinical recommendations (eviQ) for *MLH1/MSH2* carriers applicable before March 2019[16] (eviQ recently [21 Mar 2019] updated its recommendations for colonoscopic surveillance schedule) ○ Probands undertake annual colonoscopic surveillance from age at CRC diagnosis until age 70[16] ○ Relatives undertake annual colonoscopic surveillance from age 25 (or from the age when LS was confirmed) until age 70[16] ○ Adherence by probands and relatives: we assumed 90% initial adherence and 80%[8,17] for each subsequent colonoscopy • Prophylactic colectomy uptake in confirmed LS carriers is assumed to be nil, based on expert clinical experience (personal communication, Finlay Macrae, Royal Melbourne Hospital, 2018) • Sensitivity analysis and supplementary analysis were performed on colonoscopic surveillance adherence rate
Treatment and survival	• We assumed the extent of surgery in LS-CRC cases is the same as for non-LS-CRC cases, based on expert clinical experience (personal communication, Finlay Macrae, Royal Melbourne Hospital, 2018) • CRC mortality ○ We used stage-specific CRC survival at 5 years in Australia[17] ○ The 5-year survival from stage I/II CRC for LS carriers is 43% higher than in non-LS-CRC cases at the same stage disease[18] ○ The 5-year survival for stage III/IV CRC for LS carriers is the same as in non-LS-CRC cases (the effect of this assumption was assessed in sensitivity analysis)[19] • The population life tables were used for calculating other cause of death • Sensitivity analysis was performed on the potential survival benefit from new immune checkpoint inhibitor therapy for stage IV CRC with dMMR
Costs	• Germline genetic testing cost for each of proband and relatives was based on recent MSAC application 1504[20] • Cost of dMMR IHC test: Based on the MBS 2017 (MBS item 72847)[21] • Cost of MSI, *BRAF* V600E and *MLH1* promoter hypermethylation: Based on fees from the state of South Australia which processes large volumes of samples sent out from other states (personal communication, Nicola Poplawski, SA Pathology, 2018) • Genetic counselling ○ Genetic counselling for probands is assumed to be performed via oncologists/treating clinicians, therefore does not incur cost ○ Genetic counselling for relatives is performed by a genetic counsellor and the consultation cost was based on the Medicare Benefits Schedule 2017 (MBS item 132)[22] • We assumed that colonoscopy is associated with 0.27% of non-fatal adverse events.[17]

Specification	Key assumption
	Costs for colonoscopy involving major complications that require hospitalisation were applied to the adverse event • Cancer treatment cost: We used aggregated stage-specific treatment costs obtained from a published study conducted in Australia.[17,23] Initial CRC treatment costs for the proband were not considered in the analysis, as they were assumed to be not affected by LS testing • Sensitivity analysis was performed on the cost for diagnostic germline gene panel test, cancer treatment cost and colonoscopy cost
Utilities	Utilities were not incorporated because of a lack of comprehensive data on the utilities associated with each step of the clinical pathway required to implement routine LS testing

CRC = colorectal cancer; dMMR = mismatch repair deficiency; IHC = immunohistochemistry; LS = Lynch syndrome; MSAC = Medical Services Advisory Committee; MSI = microsatellite instability

4. Detailed assumptions for the natural history model of colorectal cancer (CRC)

We adopted the approach of the Health Technology Assessment (HTA) reports in the UK,[7,8] and used published parameters to develop our natural history model.

1) CRC incidence

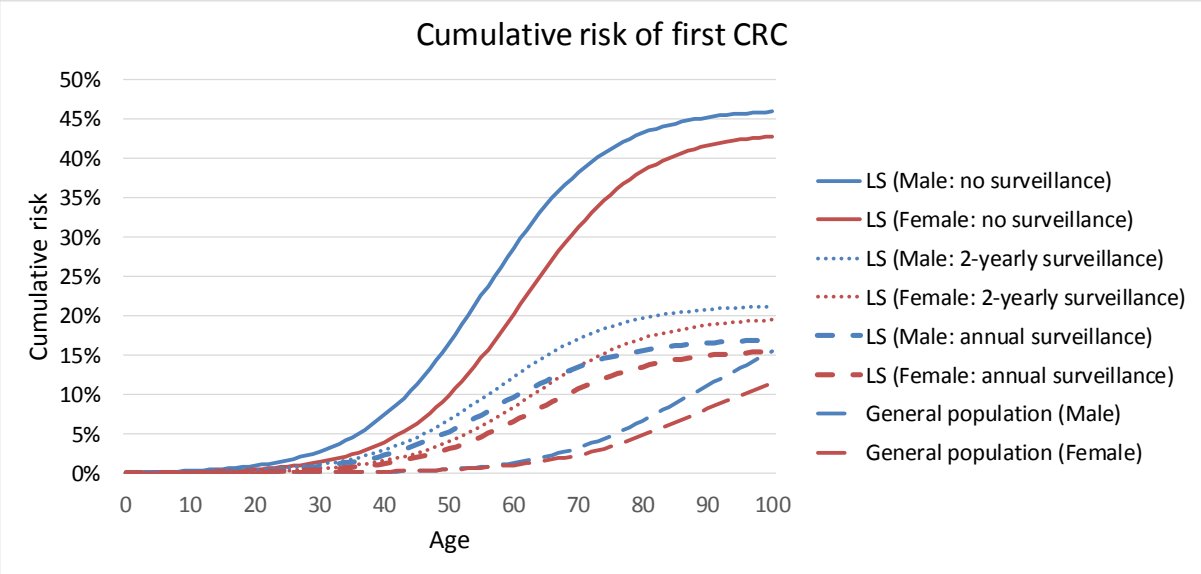
CRC development in LS carriers was modelled as a single transition from well to invasive CRC. Firstly, the overall cumulative CRC risk for LS carriers up to age 80 years with any of the four MMR gene mutations and without a personal history of CRC was obtained separately for men and women from Bonadona et al.[5] In this study, LS carriers were censored at the time of first colonoscopy, so we assumed that the reported cumulative risks of first CRC were in the absence of colonoscopic surveillance. We then assumed that colonoscopic surveillance reduces the incidence of first CRC by 61% with 2–3 yearly colonoscopic surveillance and 70% with annual surveillance (see section 4.6 for details).[4,7,8,24-27] The risk of metachronous CRC in LS carriers without colonoscopic surveillance 30 years after the first CRC diagnosis is 84%,[28] but colonoscopic surveillance is assumed to reduce the annual risk by 47%, resulting in a cumulative risk at 30 years of 62%.[9]

CRC incidence rates for individuals without LS were based on Australian 2014 sex- and age-specific CRC incidence (the latest available data on CRC incidence at the time of analysis[6]); we assumed CRC incidence had not changed since 2014. 55% of CRC cases were men.[6] Figure 1 depicts the cumulative risks of first CRC in people with LS, with and without colonoscopic surveillance, as well as in the general population for men and women.

We assumed the overall prevalence of LS carriers among people with incident CRC (all ages) is 2.8%,[10] with the proportion being greater at younger ages (diagnosis before 50 years of age, 8.4%; diagnosis at or beyond 70 years, 1.1%). As with the population-based CRC cases, we assumed that 55% of LS carriers are men.[6]

In our model, CRC incidence rates depend on age, sex, prior CRC, time since first CRC, LS status and regular colonoscopic surveillance; individuals can develop up to 2 CRCs in their lifetime (up to one metachronous CRC).

Figure 1. CRC incidence in the general population and among LS carriers



2) CRC stage

We assumed that CRC stage on diagnosis is independent of age, sex, LS status, or whether it is the first or a metachronous CRC. Colonoscopic surveillance only affects the stage at diagnosis (ie, downstages). CRC stage distribution without colonoscopic surveillance was based on Australian data from before the introduction of the National Bowel Cancer Screening Program.[29] CRC stage distribution with colonoscopic surveillance was based on a Finnish study that reported the effect of 2–3-yearly colonoscopic surveillance.[30]

3) CRC site

We grouped recto-sigmoid cancer (International Classification of Diseases, 10th revision, code C19) with rectal cancer. We assumed the site of first CRC depends on LS status. We assumed colon cancer is more predominant among LS carriers than the general population (94% among LS carriers *v* 63% (men) and 72% (women) in the general population).[6-8,31] Site of metachronous CRC was assumed to depend on previous surgery type.[7,8,31]

4) CRC mortality

We used stage-specific CRC survival at 5 years for people with CRC[17], as a person who survives 5 years with a tumour is no longer at risk of mortality from the tumour but is still at risk of a subsequent tumour. It was assumed that 5-year survival with stage I/II CRC in LS carriers is 43% better than in non-LS-CRC cases at the same stage of disease[18] but that the survival with stage III/IV CRC in LS carriers is the same as in non-LS-CRC cases.[19] In the sensitivity analysis, we assumed that survival at 5 years for LS carriers with stage IV CRC was 20% higher, to reflect the potential benefit of new treatments being developed, such as immunotherapy targeting advanced/metastatic disease with mismatch repair deficiency (dMMR).

5) Other cause mortality

The overall population life table is used for calculating other causes of death. Death from other causes was modelled by using mortality rates in 2011 Australian life tables, separately for men and women and adjusted to remove the proportion attributable to CRC, estimated by dividing the number of deaths from CRC in each age group by the total number of deaths in that age group in 2011 Australian mortality data. We used the same other cause mortality rates for LS carriers.

6) Colonoscopic surveillance

A controlled trial in Finland of 3-yearly colonoscopic screening compared with no screening targeting asymptomatic LS families, including both mutation-positive and -negative family members, found that 3-yearly colonoscopic surveillance is effective in reducing CRC incidence in LS carriers.[4]

Recently published overseas guidelines recommend 1–2-yearly colonoscopic surveillance of LS carriers, in view of the high rate of interval CRCs in LS carriers undergoing surveillance with intervals exceeding 3 years.[32] In Australia, the eviQ clinical guidelines recommend annual colonoscopic surveillance for LS carriers, but the recommended starting and stopping ages and surveillance interval varies by the MMR gene mutation: i) *MLH1*/*MSH2*: annual colonoscopy from age 25 (or from 5 years less than age of youngest affected if under 30) until age 60 years, then either continue annual surveillance or reduce the surveillance frequency to 2-yearly; ii) *MSH6*/*PMS2*: annual colonoscopy from age 30 (5 years less than age of youngest affected if under 35) until age 60 years, then either continue annual surveillance or reduce the surveillance frequency.[16]

In its recently updated recommendations (21 March 2019), eviQ recommends slightly less intensive surveillance: colonoscopy every 1–2 years, with a review of colonoscopy frequency at age 60 years. The updated eviQ also recommends that colonoscopy starts at: i) age 25 for *MLH1/MSH2* carriers; ii) age 25–30 years for *MSH6* carriers; and iii) age 35 years for *PMS2* carriers. These recommendations are not reflected in our analyses, which pre-date these changes in recommendations.

No study has compared the effectiveness of different colonoscopic surveillance intervals at the time of this analysis. Additional factors that need to be considered when comparing assessments of the effect of colonoscopic surveillance interval in patients with LS include adherence to colonoscopic surveillance, developments in colonoscopy technology and quality training, polypectomy rate, adenoma detection rate, and time since last colonoscopy to CRC incidence.

The estimated hazard ratio (HR) for first CRC in LS carriers undergoing 3-yearly colonoscopic surveillance (*v* no surveillance) was 0.387 in the Finnish study.[4,7,8] We conservatively assumed that the HR for 2-yearly colonoscopic surveillance is the same.[4,7,8,33] Jarvinen et al. reported that the cumulative 10-year CRC risk in asymptomatic LS families in Finland (1982–1998) was 13% with 3-yearly colonoscopic surveillance.[4] The corresponding cumulative risk with 2–3-yearly colonoscopic surveillance (1982–2009) was 12.4%.[24] We also

made a simple assumption that the HR associated with annual colonoscopic surveillance is 0.3, which resulted in a 3–4 percentage point reduction in the cumulative risk of first CRC in LS carriers to age 80 years in men (from 20% to 16%) and women (from 17% to 14%). This absolute reduction in the cumulative CRC risk is consistent with earlier studies of 1–2-yearly colonoscopic surveillance, although direct comparisons cannot be made. In the Netherlands, the reported cumulative 10-year CRC risks among confirmed LS carriers undergoing 2–3-yearly colonoscopic surveillance (1985–2003) and 1–2 yearly colonoscopic surveillance (since 1995) were 10.5% and 6% respectively.[25,26] Mecklin et al. reported that the cumulative CRC risk by age 60 among confirmed LS carriers undergoing 2–3-yearly colonoscopic surveillance (1982–2005) in Finland was 35% in men and 22% in women (ie, overall risk is 28–29%).[30] Engel et al. reported that the overall cumulative risk by age 60 in LS carriers undergoing 1–2-yearly colonoscopic surveillance in Germany (until 2007) was 23%.[27]

We also made two alternative assumptions on the effect of colonoscopy on CRC risk in LS carriers: i) colonoscopic surveillance reduces CRC incidence and downstages; ii) colonoscopic surveillance downstages only. In both cases we also assume that colonoscopic surveillance downstages both incident and metachronous CRC.

Table 2. Summary of natural history model parameters and range of parameter values used for one-way sensitivity analyses

Parameter	Baseline (sensitivity analysis: lower – upper)	Detailed assumptions
Prevalence of LS in CRC[10]		
All ages	0.028	
< 50 years	0.084	
< 60 years	0.057	
< 70 years	0.038	
≥ 70 years	0.011	
Proportion of LS gene mutated[34]		
MLH1	0.32	
MSH2	0.39	
MSH6	0.14	
PMS2	0.15	
Cumulative risk of CRC across the four MMR genes in LS carriers without colonoscopic surveillance		
Men[5,7,8]	to 20 years: nil to 30 years: 3% to 40 years: 7% to 50 years: 16% to 60 years: 29% to 70 years: 38% to 80 years: 43%	
Women[5,7,8]	to 20 years: nil to 30 years: 1% to 40 years: 4% to 50 years: 10% to 60 years: 20% to 70 years: 31% to 80 years: 38%	
CRC incidence in the general population[6]	Sex-and age-specific CRC incidence, Australia, 2014	
Hazard ratios for CRC in LS carriers undergoing colonoscopic surveillance[4,7-9]		
First CRC[4,7,8]	0.387	Based on 3-yearly surveillance reported in Jarvinen et al.[4]
Metachronous CRC[7-9]	0.533	Based on patients receiving 'appropriate' (up to 24 months between colonoscopies) and 'inappropriate' (> 24 months between colonoscopies) surveillance after the first CRC
Cumulative risk of metachronous CRC without surveillance in LS[9,28]		
< 10 years	28%	Applied the inverse of the HR associated with colonoscopic surveillance on the risk of metachronous CRC[9] to the cumulative risk of metachronous CRC in patients undergoing regular colonoscopic surveillance (eg, 62% by 30 years)[28]
11–20 years	63%	
21–0 years	84%	
CRC stage distribution without colonoscopic surveillance[29]		
Stage I	0.156	Using the approach of the UK HTA reports,[7,8] we assumed the CRC stage distribution depends only on whether or not patients undertake colonoscopic surveillance (ie, regardless of first/metachronous CRC, LS status, age, sex).
Stage II	0.369	
Stage III	0.362	
Stage IV	0.113	

Parameter	Baseline (sensitivity analysis: lower – upper)	Detailed assumptions
CRC stage distribution under colonoscopic surveillance[8,30]		
Stage I	0.686	Based on 3-yearly surveillance reported in Mecklin et al.[30]
Stage II	0.105	
Stage III	0.128	
Stage IV	0.081	
5-year overall survival for CRC (first/metachronous) in LS carriers		
Stage I	0.925 (0.869–0.925)	For baseline, we assumed that LS carriers with stage I/II CRC have better 5-year overall survival than non-LS carriers[17] at same stage of disease (HR=0.57)[18], and that LS carriers with stage III/IV CRC have similar 5-year overall survival as non-LS carriers (HR=1).[19] Sensitivity analyses: • We assumed LS carriers experience a similar 5-year overall survival for CRC as non-LS carriers with the same stage disease (HR=1).[19] • We also made a simplified assumption that LS carriers with stage IV CRC have 20% better survival at 5 years after diagnosis, reflecting the potential benefit of new treatments, such as immunotherapy targeting stage IV disease with dMMR.
Stage II	0.846 (0.730–0.846)	
Stage III	0.424	
Stage IV	0.095 (0.095–0.276)	
Site of CRC in confirmed LS carriers, depending on previous colorectal surgery[7,8,31]		
No previous surgery	Colon cancer: 0.94 Rectal cancer: 0.06	
First colon cancer and segmental resection	Colon cancer: 0.94 Rectal cancer: 0.06	
First colon cancer and colectomy	Colon cancer: 0.00 Rectal cancer: 1.00	
First rectal cancer and anterior resection	Colon cancer: 0.60 Rectal cancer: 0.40	Based on expert opinion and clinical experience (Finlay Macrae, Royal Melbourne Hospital, 2018).
First rectal cancer and proctocolectomy	Colon cancer: 0.00 Rectal cancer: 0.00	

CRC = colorectal cancer; LS = Lynch syndrome; MMR = mismatch repair; dMMR = mismatch repair deficiency; HR = hazard ratio; HTA = Health Technology Assessment

5. Detailed assumptions regarding diagnostic tests

Sensitivity and specificity of an immunohistochemistry (IHC) test for any of the four mismatch repair (MMR) genes was based on the UK HTA report that synthesised results from three population-based studies with or without applied age limits in the study population.[8] Molecular microsatellite instability (MSI) test characteristics were also based on the UK HTA report (ie, high levels of MSI [MSI-H] = positive test result).[8]

Pooled estimates of the sensitivity and specificity of the *BRAF* V600E mutation test and the *MLH1* promoter hypermethylation test were taken from Ladabaum et al. The included studies reported the test characteristics of both tests when followed by a variety of other tests, including IHC and MSI;[11] we considered only the polymerase chain reaction-based *BRAF* V600E mutation test.

We made the simplifying assumption that the sensitivity and the specificity of diagnostic gene panel testing for probands were each 100%, based on evidence that the sensitivity and the specificity of germline gene panel testing for LS is 99.4%.[12,13] Simulating the small fraction of false positives would require making the model significantly more complex without markedly affecting the outcome. We also assumed that targeted genetic testing for relatives is 100% accurate.

The impact of variants of uncertain significance (VUSs) were not included in our model. According to the five-tier classification system of the International Society for Gastrointestinal Hereditary Tumours (InSiGHT), VUS are class 3 tumours (class 1 = not pathogenic/no clinical significance; class 5 = pathogenic).[14] For managing families with VUS, who by definition do not have Lynch syndrome, InSiGHT does not recommend predictive testing of at-risk relatives, and surveillance for at-risk relatives is based on family history and other risk factors (ie, VUSs are not informative).[14] In Australia, families with VUS are currently managed according to family history and other information, and not necessarily with reference to LS (expert opinion and clinical experience, Finlay Macrae, Royal Melbourne Hospital, 2019).

In order to model cumulative CRC incidence in patients undergoing regular colonoscopic surveillance, we used data from an uncontrolled trial in Finland and applied the hazard ratio (HR) for CRC incidence in people undergoing colonoscopy surveillance.[4] We did not explicitly model colonoscopy test characteristics, as CRC incidence reduction associated with regular colonoscopic surveillance already captured the sensitivity and specificity of colonoscopy as part of the overall effectiveness of surveillance.

Table 3. Summary of diagnostic test parameters and ranges of parameter values used for one-way sensitivity analyses

Parameter	Baseline (sensitivity analysis: lower – upper)	Detailed assumptions
Diagnostic test characteristics		
MMR IHC testing[8]	Sensitivity: 0.962 (0.694–0.996) Specificity: 0.884 (0.79–0.94)	Synthesised from three population-based studies with or without age limit. VUS is considered as not-LS
Molecular MSI testing with MSI-H[8]	Sensitivity: 0.913 (0.426–0.993) Specificity: 0.837 (0.638–0.937)	Synthesised from three population-based studies with or without age limit. MSI-L and MSS are considered as negative test results.
BRAF V600E test by PCR[11]	Sensitivity: 0.96 (0.60–0.99) Specificity: 0.76 (0.60–0.87)	Pooled estimate from 11 studies that included a variety of previous tests, including IHC and MSI
MLH1 promoter hypermethylation test[11]	Sensitivity: 0.94 (0.79–0.98) Specificity: 0.75 (0.59–0.86)	Pooled estimate from 14 studies that included a variety of previous tests, including IHC and MSI
Diagnostic gene panel testing of proband	Sensitivity: 1.000 Specificity: 1.000	Simplified assumption
Predictive targeted genetic testing of relatives	Sensitivity: 1.000 Specificity: 1.000	Simplified assumption

MMR = mismatch repair; MSI = microsatellite instability; MSI-H = high microsatellite instability; MSI-L = low microsatellite instability; MSS = microsatellite stable; VUS = variant of uncertain significance.

6. Detailed assumptions regarding adherence to testing and surveillance and risk-reducing surgery

We made a few simplifying assumptions about LS testing uptake by people with incident CRC. All such patients are tested for dMMR under a universal LS testing program, except in the universal germline gene panel testing strategy. Ideally, 90% of CRC cases consent to gene panel testing in all testing strategies (assuming they are provided with appropriate information about the benefits of testing). We also assumed that 90% of probands informed their relatives of risk and suggested cascade testing (again, assuming the appropriate information is provided). Of the relatives who were referred, 78% attend genetic counselling, of whom 77% accept predictive genetic testing.[8,35]

In our model, only LS carriers confirmed by germline genetic testing are referred to colonoscopic surveillance (ie, CRC patients with dMMR who do not consent to genetic testing have standard follow-up after CRC diagnosis, although in clinical practice some patients with family histories suggestive of LS will be referred to the LS surveillance pathway). Initial adherence to colonoscopic surveillance by probands and relatives is assumed to be 90% (ie, that 10% of confirmed LS carriers never participate in surveillance) and that 80% attend further surveillance at the recommended interval.

Table 4. Summary of adherence and surveillance and risk -reducing surgery parameters, and range of parameter values used for one-way sensitivity analyses

Parameter	Baseline (sensitivity analysis: lower – upper)	Detailed assumptions
Testing attendance rates		
Proband: dMMR tumour testing uptake	1.00	We assumed every CRC is tested for dMMR if there is a universal LS testing program
Proband: Consent to genetic testing following genetic counselling	0.90 (0.80–1.00)	Simplified assumption: patients are provided with appropriate information about the benefits of testing. We also assumed that genetic counselling for the proband is mainstreamed and performed by treating clinician/oncologist.
Proband: Consent to refer relatives for genetic counselling	0.900	Simplified assumption
Relatives: Consent to genetic counselling[8,35]	0.780	Based on Manchester Familial Colorectal Cancer Registry data (lack of local data)[35]
Relatives: Consent to genetic testing following counselling[8,35]	0.770	Based on Manchester Familial Colorectal Cancer Registry data (lack of local data)[35]
Colonoscopic surveillance/risk-reducing surgery in confirmed LS carriers (proband/relatives)		
Initial adherence to colonoscopic surveillance[8,17]	0.90	Simplified assumption that 10% of confirmed LS carriers will never participate in colonoscopic surveillance
Interval adherence to colonoscopic surveillance	0.80[17] (0.70[36]–0.97[8,37])	Of those 90% confirmed LS carriers who participate in colonoscopic surveillance, 80% attend surveillance at recommended interval. Baseline assumption was based on the colonoscopic surveillance in the general population in Australia.[17] Lower and upper bounds were obtained from the Manchester Familial Colorectal Cancer Registry in the UK.[8,36,37]
Non-fatal adverse event due to colonoscopy[17]	0.0027	Costs for colonoscopy involving major complications that require hospitalisation were applied to the adverse event
Uptake of CRC risk reducing surgery by LS-confirmed relatives (e.g. total colectomy)	0.00	Expert opinion and clinical experience (Finlay Macrae, Royal Melbourne Hospital, 2018)

CRC = colorectal cancer; LS = Lynch syndrome; dMMR = mismatch repair deficiency.

7. Detailed assumptions regarding the family composition model

We assumed that all probands are unrelated. Relatives of probands in our model include the proband's siblings and their children, as well as children of LS-positive siblings with a mutation was confirmed by cascade testing.

When modelling the proband's relatives, we made a few simplifying assumptions. Firstly, we assumed relatives of each proband have not previously had CRC, although a small proportion may have previously been diagnosed with CRC. The UK HTA report investigated the impact of the prevalence of previous CRC in relatives, but found that its impact on the cost-effectiveness of testing for LS in people with incident CRC was minimal. Secondly, we assumed the age of a proband's siblings are within 10 years of the proband's age. The number of children per proband and the age of these children was based on the distribution of the number of children born to women in the mother's birth cohort, as well as upon the reported Australian fertility rates for women of the mother's age.[15] Finally, we assumed equal numbers of the proband's siblings, their children, and children of their siblings with confirmed LS.

We also assumed that cascade testing takes place within a year of the proband being diagnosed with CRC.

Table 5. Summary of family composition model parameters, and range of parameter values used for one-way sensitivity analyses

Parameter	Baseline (sensitivity analysis: lower – upper)	Details
Mean number of eligible 1st/2nd degree relatives per proband if 2nd degree relative is related through a known LS carrier	6[8] (3[34]–12[34])	Equal number of proband's siblings, children and sibling's children
Average number of 1st/2nd degree relatives per proband who underwent predictive germline genetic testing	3.24 (1.62–6.49)	90% of people with incident CRC undergo diagnostic genetic testing; 90% of those with positive test results (probands) consent to referring relatives. Of the relatives referred to genetic services, 78% attend genetic counselling, of whom 77% undergo genetic testing. The number (3.24) was calculated by multiplying the number of eligible relatives (six) by the referral rate for relatives (0.90) and the relatives' adherence rate to genetic counselling (0.78) and predictive genetic testing (0.77).
Proportion of relatives (as defined) with LS	0.44[8]	Meta-analysis. Reasons why the proportion is less than 50% include de novo mutations, non-paternity etc.
Average number of 1st/2nd degree relatives confirmed to have LS after predictive germline genetic testing	1.42 (0.71–2.86)	This was calculated by multiplying the number of relatives who took up predictive germline genetic testing (ie, 3.24) by the proportion of relatives with LS (ie, 0.44).
Age range of proband's siblings	within 10 years of proband's age	
Children per proband	0, 1, 2, 3, 4, 5, 6 or more[15]	Based on the distribution of the number of children born to women in mother's birth cohort
Age range of proband's children		Based on the number of children born to women of mother's age in 2011 in Australian statistics.[15]
Proportion of male relatives	0.51[15]	Based on male and female birth rate in Australia

CRC = colorectal cancer; LS = Lynch syndrome.

8. Detailed assumptions regarding costs

The cost of mismatch repair (MMR) immunohistochemistry (IHC) testing was based on the current Medical Benefits Schedule (MBS) fee.[21] Costs of molecular microsatellite instability (MSI), *BRAF* V600E, and *MLH1* promoter hypermethylation testing were based on SA Pathology fees, where large volumes of samples from other states are processed (personal communication, Nicola Poplawski, SA Pathology, 2018). The cost of genetic testing was based on the 2018 Medical Services Advisory Committee (MSAC) application.[20] We assumed that genetic counselling for probands does not incur an additional cost, as it will be probably undertaken by oncologists or treating clinicians, as described in the recent Australian *BRCA* 1/2 testing policy (mainstreaming).[38] The cost of genetic counselling for relatives was based on MBS item 132.[22] The stage-specific costs of CRC were modelled as previously described.[17,23] Initial CRC treatment costs for the proband were not considered in the analysis, as they were assumed to not be affected by LS testing.

Table 6. Summary of cost parameters, and range of parameter values used for one-way sensitivity analyses

Parameter	Baseline (sensitivity analysis: lower–upper)	Detailed assumptions
Cost of tumour testing		
MMR IHC[21]	$89.40 ($89.40–$378.00)	Baseline cost: MBS item 72847 (4–6 antibodies per specimen), 2017. Cost for sensitivity analysis based on personal communication from Nicola Poplawski, SA Pathology, 2018
Molecular MSI test	$554.00	Personal communication from Nicola Poplawski, SA Pathology, 2018
BRAF V600E test by PCR	$378.00	Personal communication from Nicola Poplawski, SA Pathology, 2018. Most FCCs in Australia send methylation and *BRAF* tests to SA Pathology or the Peter MacCallum Cancer Centre in Melbourne.
MLH1 promoter hypermethylation test	$378.00	Personal communication from Nicola Poplawski, SA Pathology, 2018). Most FCCs in Australia send methylation and *BRAF* tests to SA Pathology or Peter MacCallum Cancer Centre in Melbourne.
Cost of germline genetic testing and genetic counselling		
Proband: diagnostic gene panel testing[20]	$1200.00 ($600.00–$1200.00)	Baseline cost was based on the proposed costing, MSAC application 1504.[20] Cost for sensitivity analysis based on expert opinion for current four MMR gene panel testing cost for LS (Finlay Macrae, Peter McCallum Cancer Institute, 2018).
Relatives: predictive targeted genetic testing for relatives[20]	$400.00	Based on proposed costing, MSAC application 1504.[20]
Proband: genetic counselling[38]	$0.00	Baseline cost based on the recent *BRCA* testing policy, which recommends genetic counselling for proband be performed by oncologists or treating clinicians (mainstreamed)
Relatives: genetic counselling[22]	$263.90	Based on MBS item 132 (2017 schedule)[22]
Cost of colonoscopic surveillance		
Colonoscopy without complication	$1800.00 ($1440.00–$2500.00)	Included the cost of specialist visit, colonoscopy, and biopsy and polypectomy (if required).

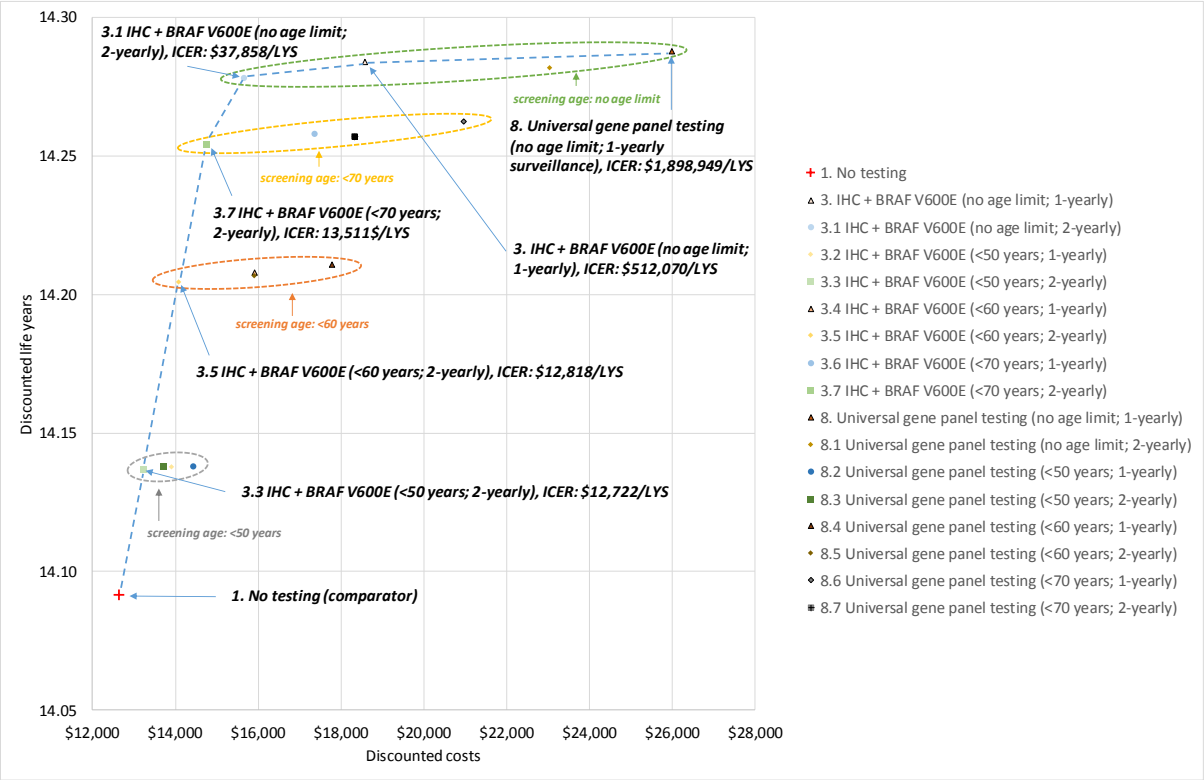
Parameter	Baseline (sensitivity analysis: lower–upper)	Detailed assumptions
(with/without polypectomy)[17]		
Colonoscopy with complication (with/without polypectomy)[17]	$16 668.01	Inflated cost of AR-DRG item G48A $12 881 based on CPI (consumer price index, health-related, the latest year available) in health in 2011–12 (100.0) and in Dec. 2017 (129.4)[39]
CRC treatment cost[23]		
Stage I: colon/rectal cancer	$38 569.51 ($38 569.51–$39 260.32)	Stage-specific CRC treatment cost included the costs of initial treatment, follow-up appointments, blood tests and imaging, treatment for relapsed disease, and palliative care, assuming 5-year risk of recurrence for each stage: • Stage I colon/rectal cancer: 6% • Stage II colon cancer: 13% • Stage III colon cancer: 30% • Stage II/III rectal cancer: 32% Treatment cost in sensitivity analysis also included cost of bevacizumab. Inflated cost based on CPI (consumer price index, health-related, the latest year available) in health in June 2014 (115.2) and in Dec. 2017 (129.4)[39]
Stage II: colon cancer	$49 172.00 ($49 172.00–$50 668.19)	
Stage III: colon cancer	$89 159.07 ($89 159.07–$92 611.98)	
Stage II/III: rectal cancer	$96 956.77 ($96 956.77–$100 639.95)	
Stage IV: colon/rectal cancer	$79 926.97 ($79 926.97–$91 437.05)	

CPI = consumer price index; CRC = colorectal cancer; DRG = Diagnosis related groups; FCC = familial cancer centre; IHC = immunohistochemistry; MMR = mismatch repair; MSAC = Medical Services Advisory Committee; PCR = polymerase chain reaction; RCPA = Royal College of Pathologists of Australasia.

9. Supplementary analysis: lower adherence rate to subsequent colonoscopic surveillance

The scenarios in this supplementary analysis are the same considered in the main stage 2 analysis (ie, combination of different testing age and colonoscopic surveillance interval on IHC + *BRAF* V600E test as well as universal gene panel testing) but explored the effect of a lower adherence rate for subsequent colonoscopic surveillance at recommended intervals (ie, 70% instead of 80%). The initial adherence rate of 90% to colonoscopic surveillance was not changed.

Figure 2. Discounted costs and life-years saved associated with testing for Lynch syndrome (LS) in people with incident colorectal cancer (CRC) diagnosed in 2017 in Australia



Strategies that are not on the dotted line are dominated (i.e. it has either higher costs or a higher cost per LYS than a more effective strategy).

Table 7. Summary results: health economic outcomes associated with testing for Lynch syndrome (LS) in people with incident colorectal cancer (CRC) diagnosed in 2017 in Australia, compared with no testing (per 1000 people with incident CRC with LS and 1420 relatives with confirmed LS), assuming a lower colonoscopy surveillance adherence rate (70% instead of 80%)

Strategy	Testing strategy (age range for testing; colonoscopic surveillance interval)	Discounted costs ($)*	Discounted life-year saved (LYS)*	Cost-effectiveness compared to no testing ($/LYS)	ICER ($/LYS)†
Testing strategies considered in the 2nd stage analysis					
1	No testing	$12 640	14.0917	-	-
3.3	IHC + *BRAF* V600E (< 50 years; 2 years)	$13 218	14.1371	$12 736	$12 722
3.2	IHC + *BRAF* V600E (< 50 years; 1 year)	$13 912	14.1377	$27 650	Dominated
8.3	Universal gene panel testing (< 50 years; 2 years)	$13 714	14.1380	$23 214	Dominated
8.2	Universal gene panel testing (< 50 years; 1 year)	$14 426	14.1383	$38 333	Dominated
3.5	IHC + *BRAF* V600E (< 60 years; 2 years)	$14 082	14.2045	$12 782	$12 818
8.5	Universal gene panel testing (< 60 years; 2 years)	$15 916	14.2066	$28 526	Dominated
3.4	IHC + *BRAF* V600E (< 60 years; 1 year)	$15 922	14.2080	$28 221	Dominated
8.4	Universal gene panel testing (< 60 years; 1 year)	$17 786	14.2109	$43 200	Dominated
3.7	IHC + *BRAF* V600E (< 70 years; 2 years)	$14 753	14.2542	$13 009	$13 511
8.7	Universal gene panel testing (< 70 years; 2 years)	$18 335	14.2568	$34 507	Dominated
3.6	IHC + *BRAF* V600E (< 70 years; 1 year)	$17 352	14.2580	$28 335	Dominated
8.6	Universal gene panel testing (< 70 years; 1 year)	$20 968	14.2624	$48 808	Dominated
3.1	IHC + *BRAF* V600E (no age limit; 2 years)	$15 662	14.2782	$16 206	$37 858
8.1	Universal gene panel testing (no age limit; 2 years)	$23 034	14.2817	$54 722	Dominated
3	IHC + *BRAF* V600E (no age limit; 1 year)	$18 580	14.2839	$30 915	$512 070
8	Universal gene panel testing (no age limit; 1 year)	$25 986	14.2878	$68 073	$1 898 949

ICER = incremental cost-effectiveness ratio; IHC = immunohistochemistry; MSI = microsatellite instability; LYS = life -years saved.

* Costs and life years are discounted by 5%.

† Relative to the next most cost-effective strategy. "Dominated" indicates that a strategy has either higher costs or a higher cost per LYS than a more effective strategy.

Table 8. Summary results on lifetime discounted costs associated with testing for Lynch syndrome (LS) in people with incident colorectal cancer (CRC) diagnosed in 2017 in Australia, compared to no testing (per 1000 people with incident CRC with LS and 1420 relatives with confirmed LS), assuming a lower colonoscopy surveillance adherence rate (70% instead of 80%)

Strategy	Testing strategy (age range for testing; colonoscopic surveillance interval)	Cost					
		Total	Proband gene panel testing (% of total cost)	Relative genetic testing and counselling (% of total cost)	dMMR tumour testing (% of total cost)	Cancer treatment* (% of total cost)	Colonoscopy (% of total cost)
Testing strategies considered in the 2nd stage analysis							
1	No testing	$110 474 000	—	—	—	$110 474 000	—
3.3	IHC + *BRAF* V600E (< 50 years; 2 years)	$113 975 000	$397 131 (< 1%)	$459 065 (< 1%)	$529 795 (< 1%)	$104 926 000 (92%)	$7 662 690 (7%)
3.2	IHC + *BRAF* V600E (< 50 years; 1 year)	$120 974 000	$397 157 (< 1%)	$459 087 (< 1%)	$529 536 (< 1%)	$104 430 000 (86%)	$15 158 700 (13%)
8.3	Universal gene panel testing (< 50 years; 2 years)	$115 756 000	$2 737 570 (2%)	$459 038 (< 1%)	—	$104 799 000 (91%)	$7 760 580 (7%)
8.2	Universal gene panel testing (< 50 years; 1 year)	$122 933 000	$2 737 530 (2%)	$459 055 (< 1%)	—	$104 392 000 (85%)	$15 344 600 (12%)
3.5	IHC + *BRAF* V600E (< 60 years; 2 years)	$117 141 000	$1 159 990 (1%)	$1 175 880 (1%)	$1 139 820 (1%)	$96 582 400 (82%)	$17 083 400 (15%)
8.5	Universal gene panel testing (< 60 years; 2 years)	$123 780 000	$9 014 080 (7%)	$1 176 250 (1%)	—	$96 315 600 (78%)	$17 273 600 (14%)
3.4	IHC + *BRAF* V600E (< 60 years; 1 year)	$132 670 000	$1 160 070 (1%)	$1 175 660 (1%)	$1 139 840 (1%)	$95 534 300 (72%)	$33 660 000 (25%)
8.4	Universal gene panel testing (< 60 years; 1 year)	$139 570 000	$9 014 060 (6%)	$1 176 600 (1%)	—	$95 344 700 (68%)	$34 035 000 (24%)
3.7	IHC + *BRAF* V600E (< 70 years; 2 years)	$119 011 000	$2 005 360 (2%)	$1 789 680 (2%)	$1 938 050 (2%)	$90 396 400 (76%)	$22 881 300 (19%)
8.7	Universal gene panel testing (< 70 years; 2 years)	$131 997 000	$17 064 500 (13%)	$1 790 430 (1%)	—	$90 032 400 (68%)	$23 109 300 (18%)
3.6	IHC + *BRAF* V600E (< 70 years; 1 year)	$139 588 000	$2 005 420 (1%)	$1 789 830 (1%)	$1 938 200 (1%)	$88 945 400 (64%)	$44 908 700 (32%)
8.6	Universal gene panel testing (< 70 years; 1 year)	$152 797 000	$17 064 400 (11%)	$1 790 830 (1%)	—	$88 601 200 (58%)	$45 341 100 (30%)
3.1	IHC + *BRAF* V600E (no age limit; 2 years)	$121 947 000	$3 386 340 (3%)	$2 163 950 (2%)	$3 665 340 (3%)	$87 264 900 (72%)	$25 466 300 (21%)
8.1	Universal gene panel testing (no age limit; 2 years)	$148 732 000	$34 008 000 (23%)	$2 164 780 (1%)	—	$86 854 800 (58%)	$25 704 000 (17%)
3	IHC + *BRAF* V600E (no age limit; 1 year)	$144 617 000	$3 386 230 (2%)	$2 163 670 (1%)	$3 665 480 (3%)	$85 635 700 (59%)	$49 766 000 (34%)
8	Universal gene panel testing (no age limit; 1 year)	$171 596 000	$34 007 800 (20%)	$2 165 110 (1%)	—	$85 210 900 (50%)	$50 212 200 (29%)

ICER = incremental cost-effectiveness ratio; IHC = immunohistochemistry; MSI = microsatellite instability; LYS = life -years saved.

* Initial CRC treatment costs for the proband were not considered in the analysis, as they were assumed to not be affected by LS testing.

Table 9. Summary results: health outcomes and resources associated with testing for Lynch syndrome (LS) in people with incident colorectal cancer (CRC) diagnosed in 2017 in Australia, compared with no testing (per 1000 people with incident CRC with LS and 1420 relatives with confirmed LS), assuming a lower colonoscopy surveillance adherence rate (70% instead of 80%)

Strategy	Testing strategy (age range for testing; colonoscopic surveillance interval)	Cancer cases	Cancer deaths	Number of colonoscopies	Cancer deaths averted	Number of colonoscopies to avert one death
Testing strategies considered in the 2nd stage analysis						
1	No testing	1566	630	—	—	—
3.3	IHC + *BRAF* V600E (< 50 years; 2 years)	1509	590	4153	40	104
3.2	IHC + *BRAF* V600E (< 50 years; 1 year)	1500	588	8216	42	198
8.3	Universal gene panel testing (< 50 years; 2 years)	1509	589	4206	41	103
8.2	Universal gene panel testing (< 50 years; 1 year)	1500	588	8317	42	199
3.5	IHC + *BRAF* V600E (< 60 years; 2 years)	1421	533	9259	97	96
8.5	Universal gene panel testing (< 60 years; 2 years)	1418	531	9362	99	95
3.4	IHC + *BRAF* V600E (< 60 years; 1 year)	1401	529	18 244	101	180
8.4	Universal gene panel testing (< 60 years; 1 year)	1400	527	18 447	102	180
3.7	IHC + *BRAF* V600E (< 70 years; 2 years)	1353	492	12 402	137	90
8.7	Universal gene panel testing (< 70 years; 2 years)	1350	490	12 525	140	89
3.6	IHC + *BRAF* V600E (< 70 years; 1 year)	1325	487	24 341	143	170
8.6	Universal gene panel testing (< 70 years; 1 year)	1322	484	24 575	146	169
3.1	IHC + *BRAF* V600E (no age limit; 2 years)	1317	473	13 803	157	88
8.1	Universal gene panel testing (no age limit; 2 years)	1314	470	13 932	160	87
3	IHC + *BRAF* V600E (no age limit; 1 year)	1286	466	26 973	163	165
8	Universal gene panel testing (no age limit; 1 year)	1282	463	27 215	166	164

ICER = incremental cost-effectiveness ratio; IHC = immunohistochemistry; MSI = microsatellite instability; LYS = life -years saved.

Table 10. Differences in selected outcomes of Lynch syndrome testing strategies on cost-effectiveness in stage 2 analysis, after reducing adherence rate for subsequent colonoscopic surveillance at recommended intervals from 80% (original assumption) to 70%*

(A) Health economic outcomes and lifetime discounted costs

Testing strategy on the cost-effectiveness frontier curve (age range for testing; colonoscopic surveillance interval)	Cost-effectiveness compared to no testing ($/LYS)		Incremental cost-effectiveness ratio		Total discounted lifetime cost (discounted by 5%)†		
	Original assumption (80% adherence)	70% adherence	Original assumption (80% adherence)	70% adherence	Original assumption (80% adherence)	70% adherence	Difference (70% minus 80%)
3.3 IHC + *BRAF* V600E (< 50 years; 2 years)	$11 536	$12 736	$11 525	$12 722	$114 170 000	$113 975 000	–$195 000
3.5 IHC + *BRAF* V600E (< 60 years; 2 years)	$11 640	$12 782	$11 711	$12 818	$117 501 000	$117 141 000	–$360 000
3.7 IHC + *BRAF* V600E (< 70 years; 2 years)	$11 780	$13 009	$12 106	$13 511	$119 303 000	$119 011 000	–$292 000
3.1 IHC + *BRAF* V600E (no age limit; 2 years)	$14 451	$16 206	$32 153	$37 858	$122 173 000	$121 947 000	–$226 000
3. IHC + *BRAF* V600E (no age limit; 1 year)	$28 926	$30 915	$411 432	$512 070	$148 193 000	$144 617 000	–$3 576 000
8. Universal gene panel testing (no age limit; 1 year)	$61 258	$68 073	$1 951 947	$1 898 949	$175 199 000	$171 596 000	–$3 603 000

(B) Health outcomes and resource

Testing strategy on the cost-effectiveness frontier curve (age range for testing; colonoscopic surveillance interval)	Number of colonoscopies			Cancer deaths averted			Number of colonoscopies to avert death		
	Original assumption (80% adherence)	70% adherence	Difference (70% minus 80%)	Original assumption (80% adherence)	70% adherence	Difference (70% minus 80%)	Original assumption (80% adherence)	70% adherence	Difference (70% minus 80%)
3.3 IHC + *BRAF* V600E (< 50 years; 2 years)	4778	4153	–625	46	40	–7	103	104	1
3.5 IHC + *BRAF* V600E (< 60 years; 2 years)	10 642	9259	–1383	112	97	–15	95	96	1
3.7 IHC + *BRAF* V600E (< 70 years; 2 years)	14 251	12 402	–1849	159	137	–21	90	90	1
3.1 IHC + *BRAF* V600E (no age limit; 2 years)	15 860	13 803	–2057	181	157	–24	88	88	0
3. IHC + *BRAF* V600E (no age limit; 1 year)	30 995	26 973	–4022	189	163	–25	164	165	1
8. Universal gene panel testing (no age limit; 1 year)	31 257	27 215	–4042	192	166	–25	163	164	1

IHC = immunohistochemistry; LYS = life -years saved.

* In this analysis, assumed initial adherence rate of 90% to colonoscopic surveillance was not changed.

† Total discounted lifetime cost includes costs of gene panel testing, relative testing and counselling, tumour testing, cancer treatment and colonoscopy.

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