# Testing for Lynch syndrome in people with colorectal cancer

## Additional analyses


### Summary

Three additional analyses were conducted using the model base case:

1. A threshold analysis on the specificity of *BRAF* V600E testing;
2. A scenario analysis in which the order of *BRAF* V600E and *MLH1* hypermethylation testing is swapped;
3. A scenario analysis in which *BRAF* V600E and *MLH1* hypermethylation testing are conducted in parallel rather than sequentially.

The specificity of *BRAF* V600E testing would need to be significantly reduced (to 34%) from the base case parameter value (76%) for the *BRAF*+methylation strategy to no longer be optimal (and for the methylation only strategy to become optimal).

The specificity of *BRAF* V600E testing would need to be reduced a little (to 73%) from the base case parameter value for the methylation only strategy to be superior to the *BRAF* only strategy.

Swapping the order of *BRAF* and methylation had a very small negative impact on cost-effectiveness (e.g., ICER increases from £11,008 to £11,017 per QALY).

Testing *BRAF* and methylation in parallel had a small negative impact on cost-effectiveness (e.g., ICER increases from £11,008 to £11,181 per QALY).

Further, an assumption in the model about the diagnostic performance of testing both *BRAF* and methylation was explored with a revised base case:

- A *BRAF* and methylation combined strategy (following IHC) remained the optimal strategy, although the ICER increased a little from £11,008 to £11,140 per QALY;
- The additional analyses described above were also conducted using the revised base case, and the results and interpretation were largely unchanged, except that the specificity of *BRAF* V600E testing would only need to reduce to 55% (from 76%) for the methylation only strategy to be optimal.

Although the sequential testing strategy outlined in the base case (IHC → *BRAF* → methylation → genetic testing) is optimal compared to other strategies considered in these analyses (at a cost-effectiveness threshold of £20,000 per QALY), the difference in ICERs (versus no testing) is generally small.

# 1 Introduction

This document describes additional analyses conducted using the economic model produced by PenTAG as the External Advisory Group (EAG) for the NICE Diagnostics Assessment programme project with the above title.

The analyses are conducted using the same simulation set as the base case analysis in the Diagnostics Assessment Report, but with changes to the diagnostic decision tree component.

Unless otherwise stated, incremental net health benefit (INHB) calculations are made assuming a cost-effectiveness threshold of £20,000 per QALY, and relative to Strategy 1 (No testing).

# 2 Additional analyses

## 2.1 Threshold analysis on the specificity of *BRAF* V600E testing

### 2.1.1 Background

The diagnostic performance parameter values in the base case analysis are given in *Table 1*. These values were drawn from a review conducted by Ladabaum et al. (2015).[1]

**Table 1: Diagnostic performance of *BRAF* V600E and *MLH1* hypermethylation testing in the model base case**

| Test | Sensitivity (%) | Specificity (%) |
|---|---|---|
| *BRAF* V600E testing | 96 | 76 |
| *MLH1* hypermethylation testing | 94 | 75 |
| *BRAF* V600E followed by *MLH1* hypermethylation testing (implicit) | 90 | 94 |

**Note:** Implicit performance of sequential testing assumes independence of tests (i.e., diagnostic performance of *MLH1* hypermethylation testing is not affected by *BRAF* V600E test result)
**Source:** Ladabaum et al. 2015[1]

A comment on the Diagnostics Consultation Document (DCD) suggests that the specificity of *BRAF* V600E testing may have been overestimated, as the stakeholder believes *MLH1* hypermethylation testing is a more specific test.

### 2.1.2 Methods

A one-way sensitivity and threshold analysis was conducted on the specificity of *BRAF* V600E testing. Strategies 3, 4 and 5 were considered:

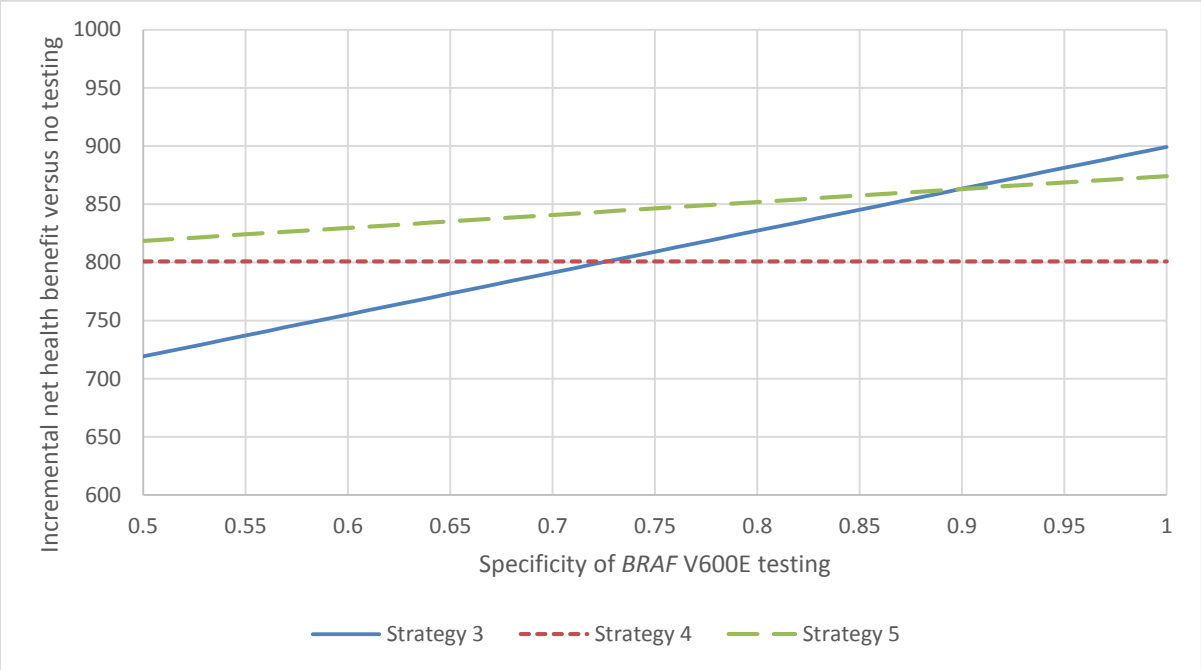
- Strategy 3: IHC (→ *BRAF* V600E) → Genetic testing;
- Strategy 4: IHC (→ *MLH1* hypermethylation) → Genetic testing;
- Strategy 5: IHC (→ *BRAF* V600E → *MLH1* hypermethylation) → Genetic testing.

The specificity of *BRAF* V600E testing was varied from 50% to 100% and the INHB of each strategy was calculated.

### 2.1.3 Results

*Figure 1* shows the impact of varying the specificity of *BRAF* V600E testing.

**Figure 1: One-way sensitivity analysis on the specificity of *BRAF* V600E testing**




The results demonstrate that:

- When the specificity of *BRAF* V600E is above 89.9%, Strategy 3 (*BRAF* only) is the optimal strategy (higher INHB than Strategies 4 and 5).
- When the specificity of *BRAF* V600E is between 72.7% and 89.9%, Strategy 5 (*BRAF* followed by *MLH1* methylation) is the optimal strategy, with Strategy 3 the next best strategy.
- When the specificity of *BRAF* V600E is between 34.1% (based on linear extrapolation) and 72.7%, Strategy 4 (*MLH1* methylation only) is the next best strategy after Strategy 5.
- When the specificity of *BRAF* V600E is below 34.1% (based on linear extrapolation), Strategy 4 is the optimal strategy.

### 2.1.4 Interpretation

The specificity of *BRAF* V600E testing has to be significantly different to the base case estimate (76%) for Strategy 5 (sequential testing) to not be optimal, and the specificity needs to be overestimated in the base case for Strategy 4 to be cost-effective.

These results are, however, based on the strong assumption that the diagnostic performance of *MLH1* hypermethylation testing is not affected by the result of *BRAF* V600E testing. This is discussed in *Section 3*.

## 2.2 Swapping the order of *BRAF* V600E and *MLH1* hypermethylation testing in sequential testing strategies

### 2.2.1 Background

In Strategies 5 and 9, patients are ruled out when they have a *BRAF* V600E mutation and/or *MLH1* hypermethylation. The order in which these tests are conducted does not affect which patients continue forward to receive genetic counselling and genetic testing, but it can affect the expected cost of the strategy.

The current ordering (testing *BRAF* V600E first) was put forward by Specialist Committee Members at the scoping stage as being the most consistent with clinical practice and expert opinion.

This analysis explores the impact of swapping the order of the tests, by looking at Strategies 5 and 9 versus Strategy 1 (no testing).

### 2.2.2 Methods

The diagnostic decision trees for Strategies 5 and 9 were changed so that *MLH1* hypermethylation testing was conducted first.

### 2.2.3 Results

The cost-effectiveness results shown in *Table 2* reveal that swapping the order results in a marginal worsening in the cost-effectiveness of the strategies, worth about 1.2 QALYs in total NHB across an annual cohort of nearly 240,000 people.

**Table 2: Cost-effectiveness results when *BRAF* V600E and *MLH1* hypermethylation testing are swapped**

| Strategy | Base case | | Swapped order | |
|---|---|---|---|---|
| 5 (IHC [→ *BRAF*/*MLH1* → *MLH1*/*BRAF*] → Genetic testing) | ICER (vs. no testing) | £11,008 | ICER (vs. no testing) | £11,017 |
| | INHB | 847.5 | INHB | 846.6 |
| 9 (MSI → *BRAF*/*MLH1* → *MLH1*/*BRAF* → Genetic testing | ICER (vs. no testing) | £11,076 | ICER (vs. no testing) | £11,092 |
| | INHB | 744.7 | INHB | 743.4 |

### 2.2.4 Interpretation

The order of testing modelled is likely to be more cost-effective than the alternative ordering. This is likely to be sensitive to the costs of *BRAF* V600E and *MLH1* hypermethylation testing. In the model these are assumed to cost £119 and £125 respectively. This finding is also sensitive to the diagnostic performance of the tests and to the prevalence of Lynch syndrome.

## 2.3 Testing *BRAF* V600E and *MLH1* hypermethylation simultaneously

### 2.3.1 Background

In Strategies 5 and 9 it is assumed (in the base case) that *MLH1* hypermethylation is only performed if *BRAF* testing does not identify a V600E mutation.

It may be that conducting these tests in parallel (i.e., not waiting for the *BRAF* result before testing *MLH1* hypermethylation) can lead to benefits, such as reduced delay before patients are diagnosed with Lynch syndrome.

To investigate this possibility, we have conducted an additional analysis in which parallel testing is conducted.

### 2.3.2 Methods

It was assumed that parallel testing has the same diagnostic performance as sequential testing, and that there are no cost savings achieved by performing the tests in parallel versus performing them independently or sequentially.

It was assumed that the full cost of each test is incurred regardless of the outcome of either test.

### 2.3.3 Results

Conducting tests in parallel is estimated to increase costs per annual cohort significantly (*Table 3*). The increase is around £326,000 for Strategy 5 and £515,000 for Strategy 9. In line with the modelling assumptions, there are no QALY gains to compensate for this.

**Table 3: Cost-effectiveness results when tests are conducted in parallel**

| Strategy | Costs | QALYs | ICER (vs. no testing) | INHB |
|---|---|---|---|---|
| 1 | — | — | — | — |
| 2 | £24,657k | 1,964 | £12,553 | 731.5 |
| 3 | £22,234k | 1,925 | £11,553 | 812.9 |
| 4 | £22,237k | 1,913 | £11,626 | 800.8 |
| 5 (Base case) | £20,750k | 1,885 | £11,008 | 847.5 |
| 5 (Parallel) | £21,076k | 1,885 | £11,181 | 831.2 |
| 6 | £25,951k | 1,874 | £13,849 | 576.3 |
| 7 | £20,362k | 1,780 | £11,438 | 762.0 |
| 8 | £20,205k | 1,743 | £11,589 | 733.2 |
| 9 (Base case) | £18,486k | 1,669 | £11,076 | 744.7 |
| 9 (Parallel) | £19,001k | 1,669 | £11,385 | 719.0 |
| 10 | £50,082k | 1,935 | £25,884 | −569.2 |

### 2.3.4 Interpretation

The additional costs of testing in parallel are significant. Though there may be the potential for QALY gains due to testing in parallel which have not been modelled, these would need to be significant.

# 3 Revised assumption for the base case

An assumption was made in the economic evaluation that the diagnostic performance of *MLH1* hypermethylation testing is not affected by the result of *BRAF* V600E testing. This assumption may be incorrect.

It is known that *BRAF* V600E and *MLH1* hypermethylation are positively associated in colorectal cancer,[2] but it is possible that this association is due only to Lynch syndrome.

A systematic review of the correlation of tumour *BRAF* mutations and *MLH1* methylation with germline MMR mutations found three studies that investigated all these in all tumours.[3] A total of 107 tumours were included, of which 35 had an MMR mutation. The sensitivity and specificity of *MLH1* methylation to detect an MMR mutation (not conditional on *BRAF* status) were 91.4% and 75.0% respectively. When this was limited to tumours without *BRAF* V600E, the specificity dropped to 60.9% (the sensitivity estimate was unchanged).

If we revise the base case of the model to incorporate reduced specificity for *MLH1* hypermethylation testing (60.9%) when conducted after *BRAF* V600E testing (i.e., when the tumour does not have *BRAF* V600E), we observe a reduced specificity for the sequential testing of *BRAF* V600E and *MLH1* hypermethylation testing (*Table 4*).

**Table 4: Diagnostic performance of *BRAF* V600E and *MLH1* hypermethylation testing in the model revised base case**

| Test | Sensitivity (%) | Specificity (%) |
|---|---|---|
| *BRAF* V600E testing | 96 | 76 |
| *MLH1* hypermethylation testing | 94 | 75 |
| *BRAF* V600E followed by *MLH1* hypermethylation testing (implicit) | 90 | 91 |

**Note:** Implicit performance of sequential testing assumes the sensitivity and specificity of *MLH1* hypermethylation testing in individuals without BRAF V600E are 94% and 61% respectively
**Source:** Ladabaum et al. 2015[1] and Parsons et al. 2012[3]

This reduced specificity results in worsened cost-effectiveness for the strategies including sequential testing (Strategies 5 and 9), because more sporadic colorectal cancer patients are offered genetic counselling and genetic testing which they do not need.

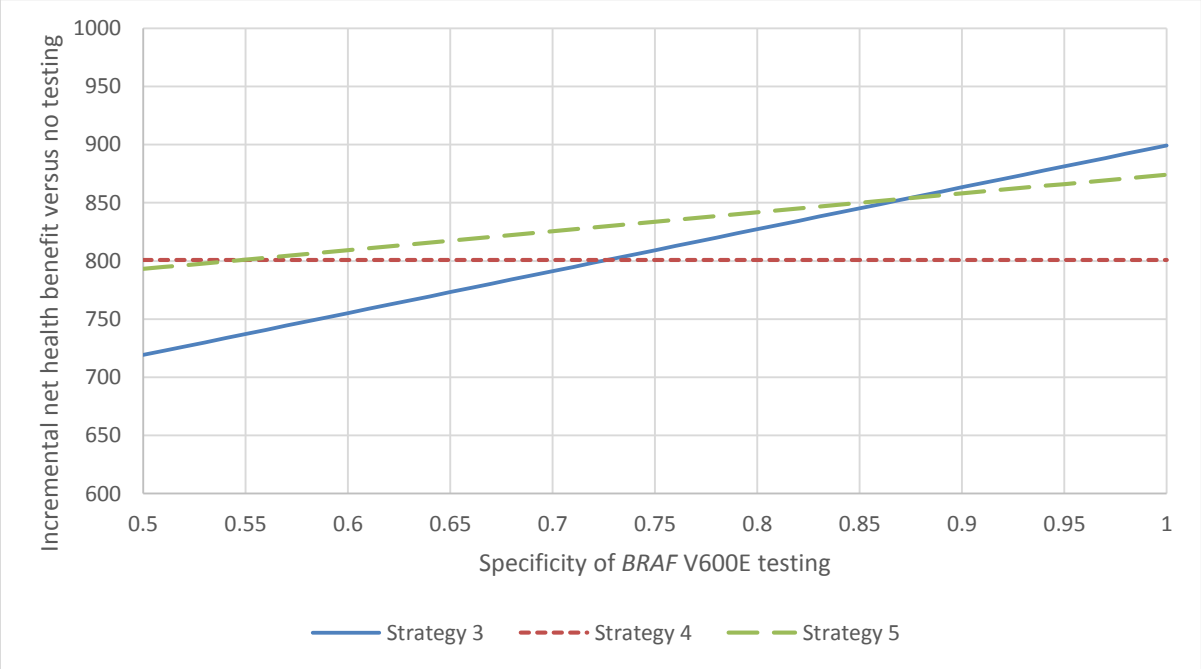
Strategy 5 (IHC [→ *BRAF* → *MLH1*] → Genetic testing) remains the optimal strategy at a cost-effectiveness threshold of £20,000 per QALY. The ICER of Strategy 5 is £11,140 per QALY. Strategy 3 (IHC [→ *BRAF*] → Genetic testing) and Strategy 2 (IHC → Genetic testing) are also on the cost-effectiveness frontier, with ICERs of £31,487 and £60,967 per QALY respectively (fully incremental ICERs).

Below, we repeat the additional analyses of *Section 2* with the revised specificity of *MLH1* methylation testing following *BRAF* V600E testing.

## 3.1 Threshold analysis on the specificity of *BRAF* V600E testing (revised base case)

*Figure 2* demonstrates similar results to *Figure 1*, but the slope of the INHB for Strategy 5 is now steeper, meaning it intercepts the INHB curve for Strategy 3 at a lower specificity value (87.3%) and the INHB curve for Strategy 4 at a higher specificity value (54.7%). Therefore there is a narrower range of values for the specificity of *BRAF* V600E testing for which Strategy 5 is optimal.

**Figure 2: One-way sensitivity analysis on the specificity of *BRAF* V600E testing (revised base case)**




## 3.2 Swapping the order of *BRAF* V600E and *MLH1* hypermethylation testing in sequential testing strategies (revised base case)

In this analysis, it is necessary to estimate the diagnostic performance of *BRAF* V600E for tumours not demonstrating *MLH1* hypermethylation. We assume that the specificity of *BRAF* V600E is reduced but sensitivity is unchanged in this case (as was the case for *MLH1* hypermethylation), and so we estimate the specificity of *BRAF* V600E as 62.43% such that the same overall diagnostic performance is achieved as shown in *Table 4*.

The results and interpretation of this analysis are largely unchanged from the original base case: the swapped order is marginally less cost-effective (*Table 5*).

**Table 5: Cost-effectiveness results when *BRAF* V600E and *MLH1* hypermethylation testing are swapped (revised base case)**

| Strategy | Revised base case | | Swapped order | |
|---|---|---|---|---|
| 5 (IHC [→ *BRAF*/*MLH1* → *MLH1*/*BRAF*] → Genetic testing) | ICER (vs. no testing) | £11,140 | ICER (vs. no testing) | £11,149 |
| | INHB | 835.3 | INHB | 834.4 |
| 9 (MSI → *BRAF*/*MLH1* → *MLH1*/*BRAF* → Genetic testing | ICER (vs. no testing) | £11,225 | ICER (vs. no testing) | £11,241 |
| | INHB | 732.6 | INHB | 731.3 |

## 3.3 Testing *BRAF* V600E and *MLH1* hypermethylation in parallel (revised base case)

The analysis from *Section 2.3* was repeated with the diagnostic performance of *BRAF V600E* and MLH1 hypermethylation in parallel assumed to be the same as the diagnostic performance in *Table 4*.

As shown in *Table 6*, Strategy 5 remains the optimal strategy (giving the greatest net health benefit), but there is still around a £326,000 additional cost to conducting the tests in parallel.

**Table 6: Cost-effectiveness results when tests are conducted in parallel (revised base case)**

| Strategy | Cost | QALYs | ICER (vs. no testing) | INHB |
|---|---|---|---|---|
| 1 | — | — | — | — |
| 2 | £24,657k | 1,964 | £12,553 | 731.5 |
| 3 | £22,234k | 1,925 | £11,553 | 812.9 |
| 4 | £22,237k | 1,913 | £11,626 | 800.8 |
| 5 (Base case) | £21,006k | 1,886 | £11,140 | 835.3 |
| 5 (Parallel) | £21,332k | 1,886 | £11,313 | 819.0 |
| 6 | £25,951k | 1,874 | £13,849 | 576.3 |
| 7 | £20,362k | 1,780 | £11,438 | 762.0 |
| 8 | £20,205k | 1,743 | £11,589 | 733.2 |
| 9 (Base case) | £18,745k | 1,670 | £11,225 | 732.6 |
| 9 (Parallel) | £19,260k | 1,670 | £11,534 | 706.9 |
| 10 | £50,082k | 1,935 | £25,884 | −569.2 |

## References


1. Ladabaum U, Ford JM, Martel M, Barkun AN. American Gastroenterological Association Technical Review on the Diagnosis and Management of Lynch Syndrome. *Gastroenterology* 2015;**149**:783-813 e20. http://dx.doi.org/10.1053/j.gastro.2015.07.037

2. Chen D, Huang JF, Liu K, Zhang LQ, Yang Z, Chuai ZR*, et al.* BRAFV600E mutation and its association with clinicopathological features of colorectal cancer: a systematic review and meta-analysis. *PLoS One* 2014;**9**:e90607. http://dx.doi.org/10.1371/journal.pone.0090607

3. Parsons MT, Buchanan DD, Thompson B, Young JP, Spurdle AB. Correlation of tumour BRAF mutations and MLH1 methylation with germline mismatch repair (MMR) gene mutation status: a literature review assessing utility of tumour features for MMR variant classification. *J Med Genet* 2012;**49**:151-7. http://dx.doi.org/10.1136/jmedgenet-2011-100714