National Institute for Health and Care Excellence

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Final

Melanoma: assessment and management

[A] Evidence reviews for genetic testing for melanoma
Health economic model report

NICE guideline NG14

Evidence reviews underpinning recommendations 1.3.8 to 1.3.14 and research recommendations in the NICE guideline

July 2022

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Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

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HE1.1 Model overview

The objective of this analysis is to compare the benefits, harms, and costs of genetic testing for BRAF V600 mutations with PCR Cobas alone versus upfront immunohistochemistry (IHC) and PCR Cobas in those testing negative with IHC in people diagnosed with stage IIC or III melanoma.

HE1.1.1 Population(s)

There are two patient populations of interest:

1. People diagnosed with stage IIC melanoma
2. People diagnosed with stage III melanoma.

The committee also made recommendations for genetic testing in other stages of melanoma, based on consensus. Please see Evidence Review A for a summary of the committee's discussion.

HE1.1.2 Interventions

There are two genetic testing approaches that the committee approved for inclusion in the research protocol. The model assesses these two mutually exclusive options:

1. PCR Cobas alone
2. Upfront immunohistochemistry (IHC) and if test negative, PCR Cobas (hereafter referred to as 'IHC & PCR Cobas')

HE1.1.3 Type of evaluation, time horizon, perspective

The analysis estimates the costs of genetic tests associated with each strategy, and measures outcomes as the number of people appropriately receiving targeted therapy. (i.e. with the BRAF mutation and are eligible for targeted therapy).

The time horizon of the model is from diagnosis to obtaining a test result. Thus, the amount of time the model will consider is only a few weeks (depends on the test turnaround time assumed for PCR Cobas). However, we also consider post-test result events such as, getting on treatment and potential recurrence occurring 2-3 years after diagnosis. These post-test result events are only included so that we can estimate the proportion of people who appropriately go on to receive targeted therapy. Therefore, the timing of events, such as recurrence or receiving treatment is largely irrelevant.

The analysis is conducted from the perspective of the NHS and Personal Social Services (PSS) in the UK.

HE1.1.4 Discounting

As we are not presenting costs or outcomes past one year, discounting is not applied.

HE1.2 Model structure

We constructed two separate decision-tree models in Microsoft Excel, one for stage IIC melanoma and one for stage III melanoma. Two different models were built as the current treatment pathways differ. Currently, those with stage IIC melanoma are only eligible for targeted therapy on recurrence, however those with stage III melanoma are immediately

eligible for adjuvant targeted therapy at diagnosis. Figure HE002 and Figure HE002 provide schematic depictions of the stage IIC and stage III model structures, respectively. Note that both models assess the expected costs and outcomes of the two competing testing approaches in a cohort of 1,000 patients.

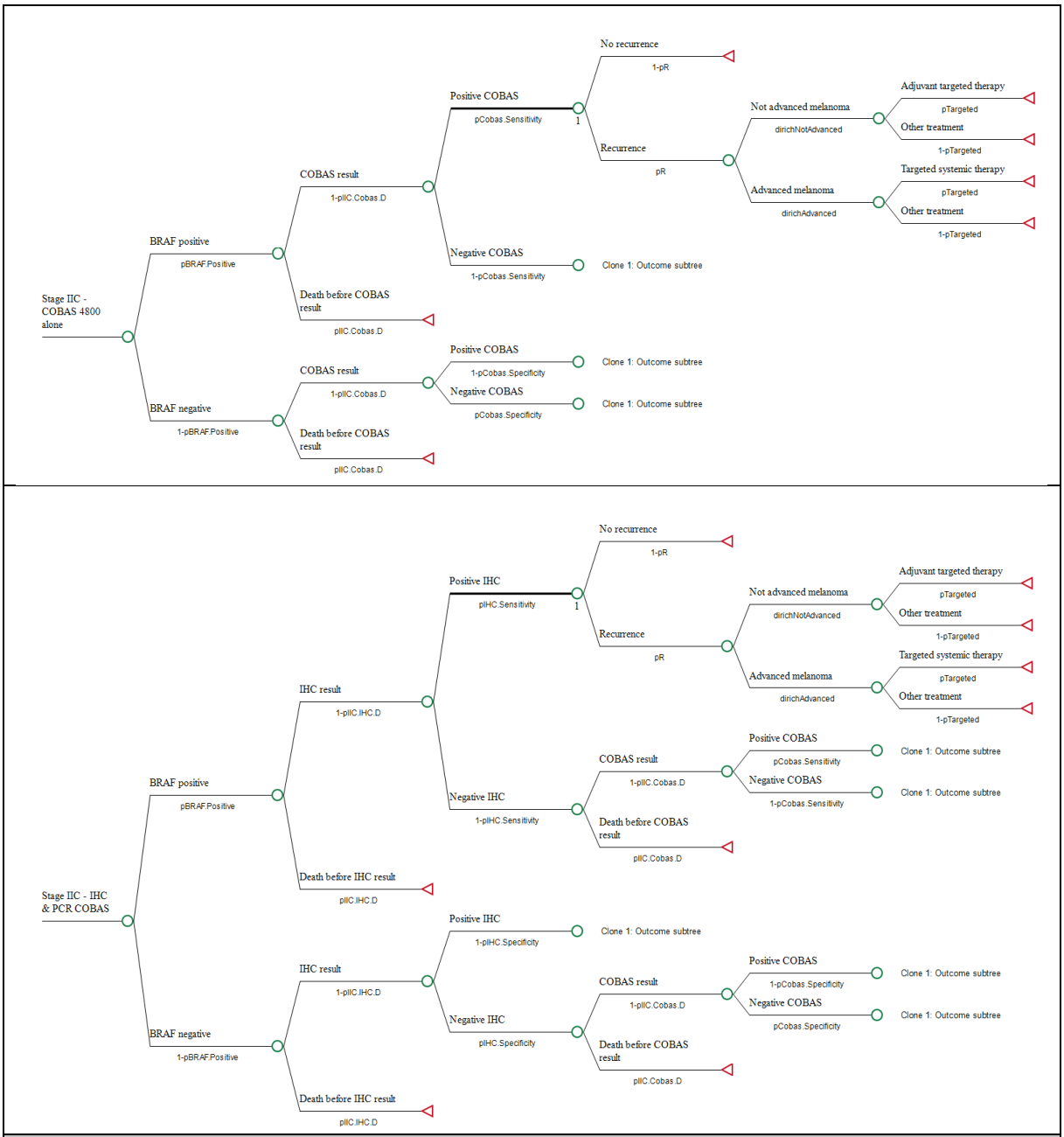
We designed the models to consider two elements, first the testing process, and second the outcomes that occur as a result of testing. With regards to the testing process, the model structure for both stage IIC and stage III are the same. For both PCR Cobas alone and IHC & PCR Cobas, the models begin with the prevalence of BRAF V600 mutations in the population. PCR Cobas alone then proceeds to get a Cobas test, and IHC & PCR Cobas then proceeds to get an IHC test.

From there, the model allows for death prior to a result, in order to capture the potential consequences of a longer test turnaround time for PCR Cobas. There is a small proportion of people who present with a high risk of rapid progression, who benefit from targeted therapies (should they be eligible) since these can provide a quick response due to their mode of action. Therefore, in addition to moving people to potentially more appropriate treatment, there is also a benefit to being able to start treatment earlier in these patients. This was expected to be a relatively small proportion of the cohort, but the committee felt it was important to capture and quantify one of the benefits of IHC testing they perceived to be clinically significant.

If the person does not die before receiving a test result, the sensitivity and specificity of each respective test are used to determine if a positive or negative result is obtained. For Cobas alone, this is the end of the testing phase of the decision tree. In the case of IHC & PCR Cobas, because IHC can only be used to test for the presence of V600E mutations, it would never be used as a standalone test, given it would miss a number of other BRAF V600 mutations. As such, if a person tests negative with IHC, they would then go on to receive a Cobas test to see if they harbour another actionable BRAF V600 mutation (V600K, V600R etc.). The decision tree then progresses as before, using the sensitivity and specificity of the Cobas test to determine if a positive or negative result is obtained in those patients initially testing negative with IHC. In contrast, if a person tests positive with IHC, they would immediately move on to the outcome phase of the decision tree.

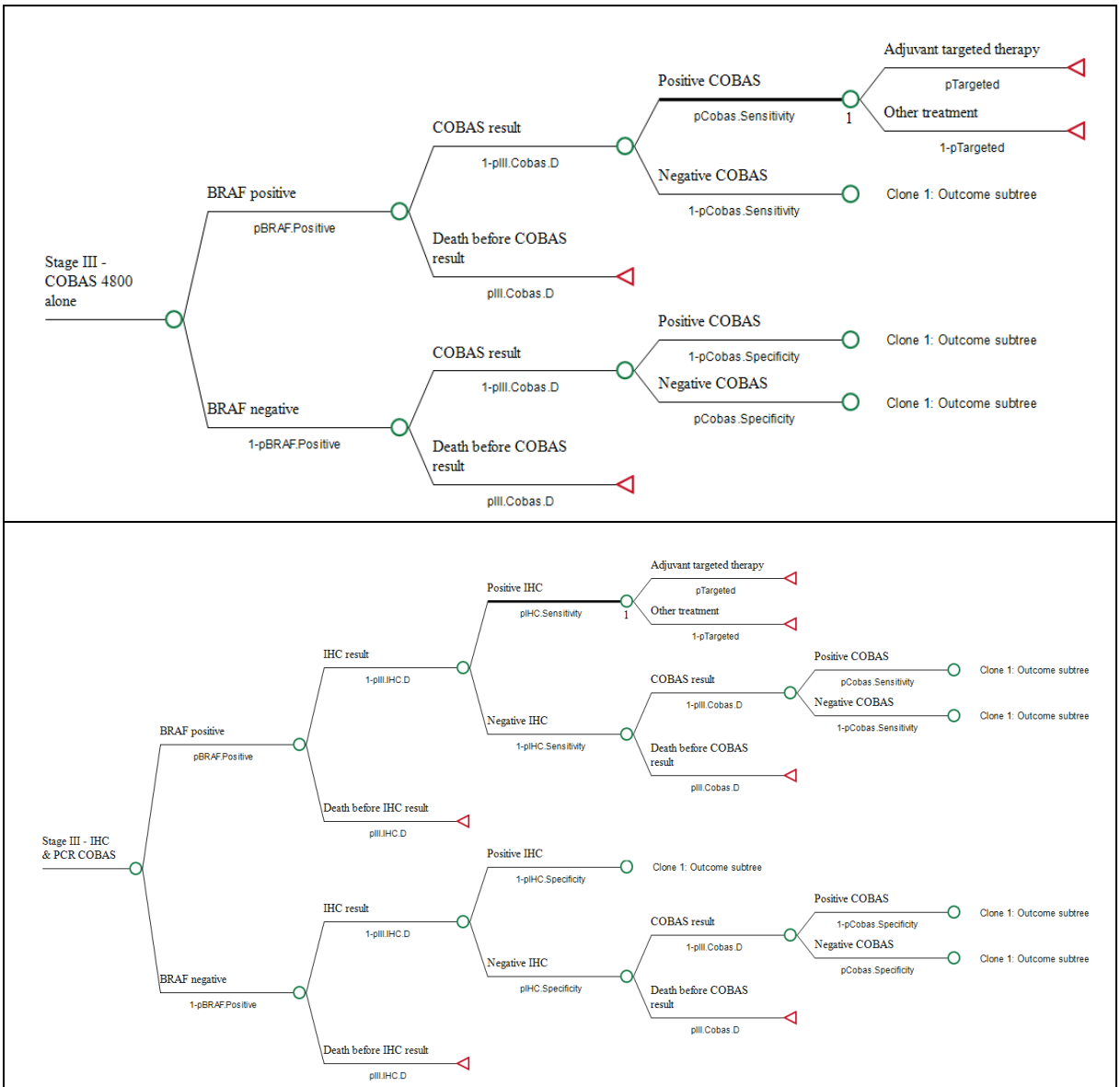
For the stage IIC decision tree, given such patients are currently only eligible to receive targeted treatment if they experience a recurrence, the outcome phase of the model then simulates the likelihood of a recurrence, the type of recurrence, and the type of treatment a person may receive if they experience a recurrence. This allows us to calculate the expected number of stage IIC patients who go on to appropriately receive targeted therapy using the two competing testing approaches.

For the stage III decision tree, as previously mentioned, the testing part of the model is identical to the stage IIC model. However, as stage III patients are immediately eligible for adjuvant treatment at diagnosis, the outcome phase of the model is simpler. After the testing phase of the model, rather than simulating if a patient experiences a recurrence, the model simply goes on to estimate the number of people who go on to receive targeted treatment or other treatments using the two competing testing approaches.



Above: Decision tree for stage IIC with PCR Cobas alone. Below: Decision tree for stage IIC with IHC & PCR Cobas. Treatment outcomes for those with stage IIC melanoma are first dependent on the prevalence of BRAF V600 mutations in the population, the probability of receiving test results, the sensitivity and specificity of each test, if a patient experiences a recurrence or not, and finally the probability of receiving targeted therapy.

Figure HE001: Structure of original cost–effectiveness model stage IIC melanoma



Above: Decision tree for stage III with PCR Cobas alone. Below: Decision tree for stage III with IHC & PCR Cobas. Treatment outcomes for those with stage III melanoma are dependent on the prevalence of BRAF V600 mutations in the population, the probability of receiving test results, the sensitivity and specificity of each test, and finally the probability of receiving adjuvant targeted therapy.

Figure HE002: Structure of original cost–effectiveness model stage III melanoma

HE1.3 Model parameterisation

HE1.3.1 General approach

HE1.3.1.1 Identifying sources of parameters

With the exception of the diagnostic accuracy of IHC, which came from the systematic review conducted for this research question (see below), we identified parameters through informal searches that aimed to satisfy the principle of 'saturation' (that is, to 'identify the breadth of information needs relevant to a model and sufficient information such that further efforts to identify more information would add nothing to the analysis' [Kaltenthaler et al., 2011]). We conducted searches in a variety of general databases, including Medline (via PubMed), the Cochrane Database of Systematic Reviews and GoogleScholar.

When searching for resource-use and cost parameters in particular, we conducted searches in specific databases designed for this purpose, the CEA (Cost-Effectiveness Analysis) Registry and the NHS Economic Evaluation Database (NHS EED) for example.

We asked the GDG to identify papers of relevance. We reviewed the sources of parameters used in the published CUAs identified in our systematic review for all review questions; during the review, we also retrieved articles that did not meet the formal inclusion criteria, but appeared to be promising sources of evidence for our model. We studied the reference lists of articles retrieved through any of these approaches to identify any further publications of interest.

In cases where there was paucity of published literature for values essential to parameterise key aspects of the model, we obtained data from unpublished sources; further details are provided below.

HE1.3.1.2 Selecting parameters

Our overriding selection criteria were as follows:

- The selected studies should report outcomes that correspond as closely as possible to the health states and events simulated in the model.
- The selected studies should report a population that closely matches the UK population (ideally, they should come from the UK population).
- All other things being equal, we preferred more powerful studies (based on sample size and/or number of events).
- Where there was no reason to discriminate between multiple possible sources for a given parameter, we gave consideration to quantitative synthesis (meta-analysis), to provide a single summary estimate.

HE1.3.2 Baseline clinical data and natural history

HE1.3.2.1 Prevalence of BRAF V600 mutations

The prevalence of BRAF V600 mutations in our model populations is a key factor to this model, as this, in combination with a testing approaches' sensitivity and specificity will help determine the number of true positives, true negatives, false positives, and false negatives. The prevalence of having a BRAF V600 mutation in our populations of interest is 34.0%. This number comes from a recent retrospective audit of UK laboratories performing BRAF genetic testing in melanoma samples (Charakidis 2020). In this audit, 14 labs participated, and 4,050 samples were tested between January to December of 2019. Of the 4,050 samples 1,377 had a BRAF V600 mutation for a prevalence of 34.0%.

HE1.3.2.2 Risk of death before a test result

The model also accounts for potential consequences occurring as a result of differences in test turnaround times for IHC compared to PCR Cobas. It does this by allowing people to either receive a test result or die before receiving a test result. To obtain the probabilities of death during the test turnaround times, we turn to a recent publication which has 5-year survival data for stage IIC melanoma and stage III melanoma (Gershenwald 2017). Using the published 5-year survival probabilities, we can calculate the 5-year probability of death, as this is the complement of 5-year survival. This process requires one extra step in the case of stage III melanoma, where we first calculate a weighted average for the 5-year survival probability across the four sub-stage categories. These calculations are detailed in Table HE001.

Table HE001: 5-year survival and death probabilities

	5-year survival (n)	5-year probability of death
Stage IIC		
	82% (691)	18%
Stage III		
IIIA	93% (1006)	-
IIIB	83% (1170)	-
IIIC	69% (2201)	-
IIID	32% (205)	-
Weighted Average	76.19% (4582)	23.81%

Using the 5-year probability of deaths from Table HE004, we then are able to calculate the daily rate of death using the following equation:

$$Daily\ Rate\ of\ Death = \frac{-ln(1 - 5yr\ probability\ of\ death)}{(365.25 * 5)}$$

However, to calculate our probability of death before receiving IHC or Cobas results, we need an estimate how long it takes to receive these results (i.e., the test turnaround times). We were unable to find a credible value in the literature, so based on committee input we assumed that IHC has a test turnaround time of 0 days and PCR Cobas has a test turnaround time of 14 days. As these figures lack empirical foundation, we fitted broad triangular distributions to vary these parameters in probabilistic analyses and tested the impact in deterministic sensitivity analysis. We can then use the daily rate of deaths, the time to get a result and the following equation to obtain the probability of death before a test result. These values are summarized in Table HE002.

$$Probability\ of\ death\ before\ test\ result = 1 - EXP(Daily\ rate\ of\ death\ x\ days\ to\ test\ result)$$

Table HE002: Rate and Probability of Death

Stage	Daily rate of death	Probability of death before Cobas[a]
IIC	0.000108666	0.001520165
III	0.000148915	0.002082638

(a) The model does account for death before IHC. However, as we assume IHC has a test turnaround time of 0 days, this means that the probability of death before a result is 0 as well.

HE1.3.3 Diagnostic accuracy

The model's only basic effectiveness parameters are the sensitivity and specificity for IHC and PCR Cobas.

The sensitivity and specificity for IHC came from the results of the clinical review and are detailed in Table HE003. However, the sensitivity and specificity of IHC are dependent on what test is used as the reference standard. The committee agreed to use next generation sequencing (NGS) for any BRAF V600 mutation as the reference standard in the base case. This is because in the clinical review, the committee saw evidence that NGS was capable of detecting BRAF V600 mutations that other tests missed. However, the committee noted that the use of NGS as the reference standard would ultimately include BRAF V600 mutations that may yet to be proven as actionable targets (i.e., targeted therapies may not have evidence of efficacy in tumours harbouring these mutations). However, the committee felt that the use of a reference standard other than NGS would exclude patients with BRAF V600 mutations that may benefit from available targeted therapies. As such, the committee

considered the use of NGS as the preferred reference standard for IHC with other sensitivity and specificity values based on other reference standards to be explored in separate sensitivity analyses.

Table HE003: IHC sensitivity and specificity

Reference standard	No. studies (sample size)	Diagnostic accuracy	
		Sensitivity	Specificity
Base case			
NGS – any BRAF (all studies)	5 (393)	0.80 (0.65, 0.90)	0.98 (0.93, 0.99)
Sensitivity analysis			
NGS – any BRAF (excluding high risk of bias studies)	4 (289)	0.83 (0.63,0.93)	0.97 (0.91, 0.99)
Cobas alone (all studies)	9 (837)	0.90 (0.86, 0.93)	0.92 (0.81, 0.97)
Cobas alone (excluding high risk of bias studies)	7 (686)	0.91 (0.86, 0.94)	0.91 (0.76, 0.97)

The sensitivity and specificity values for PCR Cobas with NGS - any BRAF mutation, as the reference standard was calculated from two studies that were included as part of the clinical review (Ihle 2014; Franczak 2017). An additional informal search was carried out to try to find additional studies where PCR Cobas was used with NGS – any BRAF mutation, as the reference standard, however no additional studies were found. These results are detailed in Table HE004.

Table HE004: PCR Cobas sensitivity and specificity

Reference standard	No. studies (sample size)	Diagnostic accuracy	
		Sensitivity	Specificity
Base case			
NGS – any BRAF (all studies)	2 (108)	0.859 (0.763, 0.920)	0.955 (0.735, 0.994)
Sensitivity analysis			
PCR Cobas[a]	-	1	1
(a) The sensitivity and specificity of PCR Cobas with PCR Cobas as the reference standard are both 1.			

Additionally, it is worth noting that the model is set so that the same reference standard is used for both tests. That is to say if NGS is used as the reference standard for IHC it is also used as the reference standard for Cobas, and if Cobas is the reference standard for IHC it is also the reference standard for Cobas. This is to ensure consistency as mixing reference standards would be inappropriate.

HE1.3.4 Outcomes occurring after testing

HE1.3.4.1 Stage IIC

Under the current pathway, those with stage IIC melanoma are only eligible to receive targeted therapies on recurrence. Thus, to calculate the number of stage IIC patients who go on to appropriately receive targeted therapy, we first must calculate the proportion of stage IIC patients who will experience a recurrence. The base case and alternative values for stage IIC recurrence in the model are detailed in Table HE005.

Table HE005: Stage IIC risk of recurrence

	Incidence % (k/N)	Population
Base case		
Lim 2018	34.38% (11/32)	UK
Sensitivity analysis		
Von Schuckmann 2019	24.39% (10/41)	Australia

The median duration of follow-up was 23.3 +/- 8.4 months for the Lim study, with a censor date at 3 years. The Von Schuckmann article was looking at the rate of recurrence over a 2-year period. This length of follow-up was considered appropriate to estimate the lifetime probability of recurrence as it has been noted previously that most recurrences occur in the first 2-3 years after treatment (Reuth 2015).

If a patient experiences a recurrence, the model then predicts the type of recurrence (e.g., advanced; unresectable stage III and stage IV, or not advanced). The base case and alternative values for the type of recurrence used in the model are detailed in Table HE006.

Table HE006: Probability by type of recurrence

	Not-advanced melanoma - Incidence % (k/N)	Advanced melanoma – Incidence % (k/N)	Population
Base case			
Lim 2018	31.71% (26/82)	68.29% (56/82)	UK
Sensitivity analysis			
Park 2017	51.85% (28/54)	48.15% (26/54)	US
Lee 2017	48.08% (25/52)[a]	51.92% (27/52)	US
Weighted Average	50%	50%	US

(a) Lee 2017 reports three types of recurrence: Local/in-transit, nodal, and systemic. For our purposes we add the local/in-transit and nodal recurrences together to obtain a value for the number of not-advanced recurrences.

Finally, we use a recent presentation to calculate the proportion of BRAF positive patients who go on to receive targeted systemic therapy (Sacco 2018). This paper is of particular use, as it not only reports the number of people who receive targeted therapy 1st line, but also the number of patients who receive targeted therapy 2nd line. This is detailed in Table HE007. We were unable to find a paper that reported the number of BRAF positive patients who go on to receive targeted therapy as adjuvant treatment. In the absence of any such paper, the committee agreed to extrapolate the proportion of BRAF positive patients who receive targeted systemic therapy for advanced disease to those who receive adjuvant targeted therapy.

Table HE007: Probability of receiving targeted therapy

	Reported value	Calculated value	Derivation
Cohort size	280 (a)	-	-
% of cohort tested for BRAF mutation	0.92 (b)	258 (c)	$a * b$
% of BRAF mutants amongst those tested	0.41 (d)	106 (e)	$c * d$
1st line therapy			
% of cohort who receive 1st line therapy	0.80 (f)	224 (g)	$a * f$
Pembrolizumab	0.46 (h)	103 (i)	$g * h$

	Reported value	Calculated value	Derivation
Nivolumab + Ipilimumab	0.26 (j)	58 (k)	$g * j$
% receiving BRAF targeted treatment	0.27 (l)	60 (m)	$g * l$
2nd line therapy			
% of patients who discontinue 1st line Pembrolizumab	0.62 (n)	64 (o)	$i * n$
% patients who discontinue Pembrolizumab who go on 2nd line treatment	0.17 (p)	11 (q)	$o * p$
2nd line is BRAF targeted treatment	0.21 (r)	2 (s)	$q * r$
% of patients who discontinue 1st line Nivolumab + Ipilimumab	0.62 (t)	36 (u)	$k * t$
% patients who discontinue Nivolumab + Ipilimumab who go on 2nd line treatment	0.41 (v)	15 (w)	$u * v$
2nd line is BRAF targeted treatment	0.63 (x)	9 (y)	$w * x$
Total			
Proportion of BRAF Patients who receive targeted treatment	-	0.6698	$\frac{m + s + y}{e}$

HE1.3.4.2 Stage III

As noted above, a source detailing the proportion of those with a BRAF mutation who go on to receive adjuvant targeted treatment was not available. As such, we again use the proportion of those with a BRAF mutation (see Table) who go on to receive systemic targeted treatment for advanced disease to estimate this parameter.

HE1.3.5 Cost and healthcare resource use identification, measurement and valuation

The cost year for our analysis is 2020.

Where possible, we drew resource-use information from the primary evidence-base identified in our systematic review of clinical evidence (see HE1.3.3 Diagnostic accuracy). In the absence of such data, we attempted to locate published economic evaluations or costing studies providing relevant information. We filled any remaining gaps with estimates from the experts on the guideline committee.

We obtained unit costs for each of the resource use elements from a number of standard sources.

- Where we cannot source an appropriate unit cost from these sources, we may use values from a relevant published study, in which case we inflate them to current prices using the CCEMG – EPPI Centre Cost Converter (CCEMG 2021).

HE1.3.5.1 Genetic testing costs

To estimate the costs of each genetic test we leveraged information from published papers and committee input. Broadly, our costing approach for each genetic test consists of three categories where costs are accrued: equipment, consumables, and staff.

To estimate the costs for PCR Cobas, we rely on a recent micro-costing publication from the Netherlands (Pasmans et al. 2019). While a UK population would have been preferable, the committee agreed to extrapolate from this paper to the UK, as there was no such paper for the UK. This paper is of particular use as its data includes costs specific to BRAF testing with the Roche Cobas platform. Specifically, it includes costs for equipment, including platform acquisition costs (capital) and annual maintenance costs, consumables, and staff. As the costs reported in this paper are in 2018 euros, they were converted and inflated to 2020 pounds sterling using the CCEMG – EPPI-Centre Cost Converter (CCEMG 2021). Both the costs extracted from Table 2 of Pasmans et al 2019 and the converted and inflated values are detailed in Table HE008.

Table HE008: Costing calculations for PCR Cobas

	Costs[a]	Converted to pounds and inflated to 2020
Equipment		
Capital per sample	€29.66	£26.96
Maintenance per sample	€17.14	£15.58
Consumables		
Consumables per sample	€7.78	£7.07
Staff		
Personnel sample preparation and primary data analysis per sample	-	£21.90[b]
Personnel data interpretation and report per sample	-	£3.69[c]
Total		
Total cost per sample	-	£75.20

(a) Equipment capital and maintenance costs and consumables costs extracted from Pasmans et al. 2019.

(b) Rather than take the costs reported for this step and convert and inflate them to 2020 pounds, we instead take the time to complete this step, 95 minutes, as reported by Pasmans et al. We then multiply this time by salary per minute, obtained from the midpoint salary for an NHS band 5 worker using the 2020 NHS agenda for change scales (Agenda 2021) to calculate the cost for this step.

(c) We use the same approach described in (b), however, this time using the time required to complete this step, 16 minutes, as reported by Pasmans et al.

To estimate the costs for IHC, we again rely on Pasmans et al. 2019 and a recent micro-costing in the UK for lynch-syndrome-associated pathogenic variants (Ryan et al. 2019). Though the costs in Ryan are not specific to BRAF testing, and thus are of limited value when it comes to calculating the cost of consumables, it provides a detailed reporting of staff time involved in conducting a IHC test obtained through direct observation. Though this testing is for a different cancer, the staff time for IHC is likely to be generalizable, regardless of the specific mutation of interest. Therefore, our approach to costing IHC utilizes the equipment costs, both capital and maintenance, from Pasmans, detailed in Table HE009, and the staff times from Ryan, detailed in Table HE010. In calculating staff costs, the data from Ryan is preferable as it comes from a UK population rather than the Netherlands. To derive the final staff costs, we emulate the approach utilized in Ryan, which, at its simplest involves multiplying the median staff time per sample for each activity by the salary per minute of the staff member completing that step. To obtain the salary per minute, as in Ryan, we take the midpoint salary, £26,970, for an NHS band 5 worker from the NHS agenda for

change (Agenda 2021) and for a 3rd year consultant, £89,809, from the British Medical Association's consultant pay scales (Pay scales 2021). Unlike Ryan, which utilizes the 2017 versions of these pay scales, we use the 2020 pay scales. These annual salaries are then converted to weekly salaries by first dividing by the number of weeks in a year, 52, and then by dividing by the number of working hours in a week, 37.5. This results in an hourly wage of £13.83 for a band 5 employee, and £46 for a 3rd year consultant. Finally, to obtain our staff cost per sample we multiply our median staff time per sample for each step by the wage per second, which is obtained by dividing our hourly wage by the total number of seconds in an hour, 3,600. Additionally, we use the consumables listed in Ryan in conjunction with advice from the committee to determine the consumables required for IHC BRAF testing, which are detailed in Table HE011.

Table HE009: Equipment cost calculations for IHC

	Costs[a]	Converted to pounds and inflated to 2020
Equipment		
Capital per sample	€1.17	£1.06
Maintenance per sample	€0.71	£0.65
Total equipment cost per sample	€1.80	£1.71
(a) Equipment capital and maintenance costs extracted from Pasmans et al. 2019.		

Table HE010: Staff cost calculations for IHC

Activity	Staff member	Median staff time per sample (hh:mm:ss)[a]	Staff cost per sample
Slide myotome MMR	NHS: 5	00:00:44	£0.17
Labeling	NHS: 5	00:01:20	£0.31
Bake	NHS: 5	00:07:30	£1.73
Loading ultra	NHS: 5	00:00:23	£0.09
Unloading ultra	NHS: 5	00:00:21	£0.08
Wash	NHS: 5	00:00:45	£0.17
Dehydration and clear	NHS: 5	00:00:23	£0.09
Checking (1/3 of slides)	NHS: 5	00:00:02	£0.01
Checking blocks	NHS: 5	00:00:06	£0.02
Scoring slides	BMA: Consultant Yr 3	00:00:58	£0.74
Total	-	-	£3.61
(a) Staff times obtained from Ryan et al. 2019.			

Table HE011: Consumables cost calculations for IHC

Item[a]	List Price[a]	Unit cost per sample	Source
IHC Antibodies[e]	-	£69.61	Derived based on committee input
Reaction Buffer[b]	£82	£0.00	Ryan et al. 2019
Acrytol[b]	£0.02	£0.02	Ryan et al. 2019
Glass slides[c]	£75.60	£0.03	NHS Supply Chain Catalogue
Cover slips[c]	£30.46	£0.03	NHS Supply Chain Catalogue

Item[a]	List Price[a]	Unit cost per sample	Source
Total[d]	-	£69.69	Committee input

(a) Consumables for IHC were obtained from the supplement of Ryan et al. 2019. As this microcosting was looking at Lynch syndrome-associated pathogenic variants in endometrial cancer rather than BRAF V600E mutations in melanoma patients, it is unlikely the antibodies listed in this paper are relevant. As such, we extracted the items likely to generalize for IHC BRAF testing, namely the reaction buffer, acrytol, glass slides and cover slips.

(b) For these items we extract the cost listed in the supplement to Ryan et al. and inflate them from 2017 to 2020 values.

(c) For these items, we take costs directly from the 2020 NHS supply chain catalogue. To obtain our unit cost per sample we divide the list price by the quantity of the item included.

(d) To calculate a total cost for IHC consumables, we work backwards. The committee reported three values for the overall cost (cost of equipment, consumables, and staff) for IHC testing, £40, £75, and £200. We take £75 as our mean cost and use the other values as our minimum and maximum value in sensitivity analysis. To obtain the total cost of consumables, we subtract our total calculated equipment and staff costs (Table HE009 and Table HE010) from £75. This gives us a value for the total cost of IHC consumables, £69.69.

(e) We continue working backwards to obtain a cost for IHC antibodies. We do this by subtracting the costs of our other consumables, that is the reaction buffer, acrytol, glass slides and cover slips from our total value to get our unit cost per sample for the IHC antibodies, £69.61.

The total cost for IHC, including equipment, consumables, and staff from our previous calculations, was estimated as £75 per test and is detailed in Table HE012.

Table HE012: Costing totals for IHC

	Costs 2020 (£)
Equipment	
Total cost per sample	£1.71
Consumables	
Total cost per sample	£69.69
Staff	
Total cost per sample	£3.61
Total	
Total cost per sample	£75

HE1.3.6 Modelling assumptions

The economic analysis makes the following assumptions:

- Recurrence rates are the same regardless of BRAF status,
- BRAF status follows the same distribution across stages,
- The sensitivity and specificity of COBAS (conditional on a negative IHC test) are the same as the sensitivity and specificity of COBAS as a first line test,
- If a patient experiences a recurrence, the probability for each type of recurrence (e.g., advanced; unresectable stage III and stage IV, or not advanced) is consistent between each modelled population.

HE1.3.7 Sensitivity analysis

HE1.3.7.1 Deterministic sensitivity analysis

We conducted deterministic one-way sensitivity analyses to identify which model parameters had a substantial impact on the overall results. The scenarios included in the analysis were chosen based on which parameters the committee felt less certain of.

Table HE013: Summary of sensitivity analyses

Section	Base-case	Scenario(s)
Sensitivity and specificity standard	• NGS	• COBAS alone
Diagnostic accuracy, study risk of bias	• All studies	• Excluding high risk of bias
BRAF positivity rate	• 0.340	• 0.339 to 0.341
Proportion of BRAF positive patients who receive targeted systemic therapy	• Source = Sacco (2018), mean 0.625	• Source = Sacco (2018), range 0.384 to 0.837 • Source = Lim (2018), mean 0.670 • Source = Lim (2018), range 0.578 to 0.756
NGS reference standard – sensitivity rate	• 0.859	• 0.763 to 0.920
NGS reference standard – specificity rate	• 0.955	• 0.735 to 0.994
Stage III 5-year survival	• 0.762	• 0.740 to 0.783
Days to COBAS result	• 14 days	• 7 to 21 days
Death before IHC	• Probability = 0.0000	• Probability = 0.0001
IHC test cost	• £75 per test	• Range between £40 and £200 per test
COBAS test cost	• £75 per test	• Range between £49 and £107 per test

HE1.3.7.2 Probabilistic sensitivity analysis

We configured the models to perform probabilistic sensitivity analysis to quantify uncertainty in the true values of input parameters. We specified probability distributions for all input variables with the exception of the unit costs for healthcare professionals and the staff time used in the costing calculations for IHC and PCR COBAS testing, and the unit cost of IHC and PCR COBAS consumables. This was due to a lack of data on the uncertainty around the parameters and that adding an arbitrary standard deviation would increase uncertainty rather than reduce it.

We decided the type of distribution with reference to the properties of data of that type (for example, we use beta distributions for probabilities that are bounded between 0 and 1 and we use gamma distributions for cost parameters that cannot be negative). Where possible, we parameterised each distribution using dispersion data from the source from which the value was obtained; where no such data were available, we gave consideration to applying plausible ranges based on committee advice and the usual properties of similar data.

For all the parameters not included in the probabilistic sensitivity analysis it was felt that not including them was unlikely to be a major limitation and scenario analysis was sufficient to investigate the uncertainty of those parameters.

HE2 Results

HE2.1 Base-case deterministic results

HE2.1.1 Clinical outcomes

The figures below illustrate the clinical outcomes predicted by the models (that is, the outputs of each decision-tree shown in Figure HE001 and Figure HE002). Figure HE003 shows outcomes relating to testing. These results are representative (i.e., the same), for both stage IIC and III melanoma. As the prevalence of BRAF V600 mutations used in the model is approximately 34%, true negatives make up the largest share of the model cohorts. Because the testing approach using IHC & PCR Cobas includes a sequence of two tests, there is an increase in both true positives and false positives compared with the testing approach of using PCR Cobas alone. The increase in true and false positives, however, also leads to a decrease in both true and false negatives with IHC & PCR Cobas.

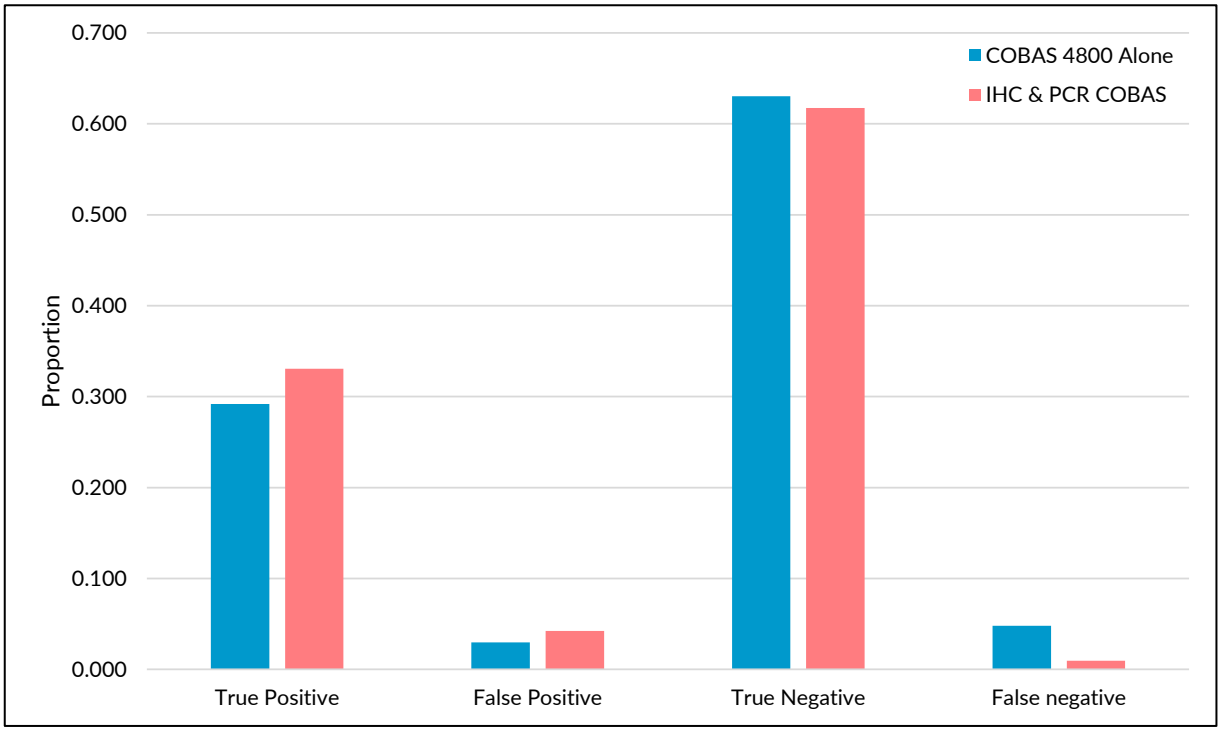


Figure HE003: Model outputs: testing results

Table HE014 provides a breakdown for all outcomes predicted for the stage IIC model cohorts. As those with stage IIC melanoma are currently only eligible for targeted treatment on recurrence, the results are stratified by those who do not have a recurrence and those who do have a recurrence. Echoing the results in Figure HE003, it is clear that the testing approach of using IHC & PCR Cobas results in an increase in true and false positives, and a reduction in true and false negatives compared with PCR Cobas alone. While small in absolute terms, IHC & PCR Cobas results in a difference of 0.4 fewer deaths before obtaining a test result for of a simulated cohort of 1,000 patients.

Table HE014: Stage IIC – outcomes for a simulated cohort of 1,000

Outcome	Testing strategy		Difference
	Cobas alone	IHC & Cobas	
Death before results	1.5	1.1	-0.4

Outcome	Testing strategy		Difference
	Cobas alone	IHC & Cobas	
No recurrence			
Appropriately eligible (TP) for targeted treatment	191.4	216.8	25.4
Appropriately ineligible (TN) for targeted treatment	413	404.7	-8.3
Inappropriately eligible (FP) for targeted treatment	19.5	27.7	8.3
Inappropriately ineligible (FN) for targeted treatment	31.4	6.3	-25.1
Recurrence			
Appropriately receives (TP) targeted treatment	67.1	76.1	8.9
Inappropriately receives (FP) targeted treatment	6.8	9.7	2.9
Appropriately receives other treatment, appropriately eligible (TP) for targeted treatment	33.1	37.5	4.4
Appropriately receives other treatment, appropriately ineligible (TN) for targeted treatment	216.3	212	-4.3
Appropriately receives other treatment, inappropriately eligible (FP) for targeted treatment	3.4	4.8	1.4
Appropriately receives other treatment, inappropriately ineligible (FN) for targeted treatment	16.5	3.3	-13.2

Abbreviations: TP, true positive; TN, true negative; FP, false positive; FN, false negative

Table HE015 is based upon the final outcomes predicted by the model, however it only shows our pre-specified outcome of interest, the number of patients who go on to appropriately receive targeted therapy, which is stratified by those who receive adjuvant targeted therapy and those who receive systemic targeted therapy for advanced disease for each genetic testing approach. Consistent with **Figure HE**003 and Table HE014 IHC & PCR Cobas as the testing approach is associated with a larger number of people going on to appropriately receive targeted therapy compared with PCR Cobas alone. This stems from the larger number of true positives identified with this testing approach. Additionally, of those who go on to targeted treatment with IHC & PCR Cobas as the testing approach, the majority do so after a positive IHC test, 19.9/24.2 and 42.8/52 for adjuvant therapy and systemic therapy for advanced disease, respectively.

Table HE015: Stage IIC – Number in cohort appropriately receiving targeted therapy

Outcome	Testing strategy		Difference
	Cobas alone	IHC & Cobas	
Adjuvant therapy			
After IHC	0	19.9	19.9
After Cobas	21.3	4.3	-17

Outcome	Testing strategy		Difference
	Cobas alone	IHC & Cobas	
Total	21.3	24.2	2.9
Systemic therapy for advanced disease			
After IHC	0	42.8	42.8
After Cobas	45.9	9.2	-36.7
Total	45.9	52	6.1
Total			
Total appropriately receiving targeted therapy	67.1	76.1	9

Table HE016 provides a breakdown for all outcomes predicted for the stage III cohorts. Unlike the stage IIC population, those with stage III melanoma are immediately eligible for adjuvant treatment. This results in a larger number of those with stage III melanoma appropriately receiving targeted therapy as this number is no longer conditional on also experiencing a recurrence. Again, like the results in Figure HE003, IHC & PCR Cobas results in an increase in true and false positives, and a reduction in true and false negatives compared with PCR Cobas alone. Furthermore, IHC & PCR Cobas results in a difference of 0.6 fewer deaths before obtaining a test result for of a simulated cohort of 1,000 patients.

Table HE016: Stage III – outcomes for a simulated cohort of 1,000

Outcome	Testing strategy		Difference
	Cobas alone	IHC & Cobas	
Death before results	2.1	1.5	-0.6
Appropriately receives (TP) targeted treatment	195.2	221.2	26
Inappropriately receives (FP) targeted treatment	19.9	28.3	8.4
Appropriately receives other treatment, appropriately eligible (TP) for targeted treatment	96.2	109.1	12.8
Appropriately receives other treatment, appropriately ineligible (TN) for targeted treatment	629	616.4	-12.6
Appropriately receives other treatment, inappropriately eligible (FP) for targeted treatment	9.8	13.9	4.2
Appropriately receives other treatment, inappropriately ineligible (FN) for targeted treatment	47.8	9.6	-38.3

Abbreviations: TP, true positive; TN, true negative; FP, false positive; FN, false negative

Table HE018 is based upon the final outcomes predicted by the model, however, as in Table it only shows our pre-specified outcome of interest, the number of patients who go on to appropriately receive targeted therapy. Again, consistent with **Figure HE**003 and Table HE016, IHC & PCR Cobas is associated with a larger number of people appropriately receiving targeted therapy compared with PCR Cobas alone. As previously mentioned, this is due to IHC & PCR Cobas having a larger number of true positives compared with PCR Cobas alone. The same pattern with stage IIC melanoma is observed again here, with the

majority of those in the IHC & PCR Cobas testing approach receiving adjuvant therapy after IHC, 182.2/221.2

Table HE017: Stage III – Number in cohort appropriately receiving targeted therapy

Outcome	Testing strategy		Difference
	Cobas alone	IHC & Cobas	
Adjuvant therapy			
After IHC	0	182.2	182.2
After Cobas	195.2	39	-156.2
Total	195.2	221.2	26

HE2.1.2 Costs

Table HE018 below details the proportion of patients who receive each test with each testing approach, as well as the cumulative costs for each approach. Under PCR Cobas alone, 100% of our simulated cohort receive PCR Cobas. With IHC & PCR Cobas, 100% of the simulated cohort receive IHC and 71.48% of the cohort also receive a PCR Cobas test. The high proportion of those receiving PCR Cobas with this approach is a result of the prevalence of BRAF V600 mutations used in the model. In the model, this figure's point estimate is 34%, leading the model to predict that 66% of our cohort do not harbour a BRAF V600 mutation (i.e., are BRAF wildtype) and that the majority of these BRAF wildtype patients will show up as BRAF negative with IHC testing. The model is structured in such a way that under this testing approach, those who test negative with IHC go on to receive a PCR Cobas test. Because most of our model cohort tests negative with IHC, the majority go on to also receive a PCR Cobas test.

Table HE018: Stage IIC & III – Costs for a cohort of 1,000

Outcome	Testing strategy		Costs	
	Cobas alone	IHC & Cobas	Cobas alone	IHC & Cobas
Receive IHC	0	1000	-	£75,000.00
Receive Cobas	1000	714.8	£75,196.92	£53,750.76
Total	1000	1714.8	£75,196.92	£128,750.76

HE2.1.3 Cost consequence analysis

Table HE019 shows base-case deterministic results for those with stage IIC and III melanoma. As detailed above, IHC & PCR Cobas is associated with more people appropriately going on to receive targeted treatment, however it is also associated with increased costs.

As detailed in Table HE019, the costs associated with stage IIC and III melanoma are the same. However, the number of people who go on to appropriately receive targeted therapy is higher for those with stage III melanoma. This is because people do not have to experience a recurrence in order to receive targeted therapy, as they are eligible for it immediately at diagnosis. In the consideration of benefits relative to costs, patients with stage III melanoma have a greater proportion of benefits to costs as the increased costs are distributed across a greater number of patients who benefit.

Table HE019: Base-case deterministic cost–utility results

Strategy	Absolute		Incremental	
	Costs	Number appropriately receiving targeted treatment	Costs	Number appropriately receiving targeted treatment
Stage IIC				
Cobas alone	£75,197	67.14	-	-
IHC & Cobas	£128,751	76.06	£53,554	8.91
Stage III				
Cobas alone	£75,197	195.22	-	-
IHC & Cobas	£128,751	221.23	£53,554	26.01

HE2.1.4 Sensitivity analysis

HE2.1.4.1 One-way sensitivity analysis

In the analyses for stage IIC (Table HE020) and stage III melanoma (Table HE021), the total cost of IHC has the largest impact on the total costs: when the cost of IHC increases from £75 to £200 per test, the additional cost of testing for an IHC and PCR strategy is £178,554 per 1,000 people tested. The majority of scenarios are associated with minor changes in the number appropriately receiving targeted therapy. However, varying the sensitivity of NGS reference standard within the limits of its 95% confidence interval had a large impact to the number appropriately receiving targeted therapy.

Table HE020: Results of the one-way deterministic sensitivity analysis – IHC & Cobas -v- Cobas alone for patients with stage III melanoma

Scenario	Base case value (range)	Incremental costs (per 1000)		Incremental benefits (per 1000)	
		Lower value	Upper value	Lower value	Upper value
Base case	-	£53,554		8.91	
Sensitivity and Specificity Standard	NGS (NGS, COBAS alone)	£53,554	£48,019	8.91	10.03
Risk of bias	All studies (All studies, Excluding high risk)	£53,554	£52,291	8.91	9.25
Rate of recurrence source	UK study (UK study, Australian study)	£53,554	£53,554	8.91	6.32
Type of recurrence source	UK study (UK study, Australian study)	£53,554	£53,554	8.91	8.91
Targeted therapy source	Sacco (Sacco, Lim)	£53,554	£53,554	8.91	8.32

BRAF positivity rate	0.340 (0.339, 0.341)	£53,608	£53,500	8.89	8.94
IIC rate of recurrence UK	0.344 (0.192, 0.514)	£53,554	£53,554	4.98	13.32
IIC rate of recurrence Aus	0.244 (0.127, 0.385)	£53,554	£53,554	8.91	8.91
Locoregional recurrence UK	0.317 (0.222, 0.421)	£53,554	£53,554	8.06	9.84
Distant recurrence UK	0.683 (0.579, 0.778)	£53,554	£53,554	7.99	9.76
Locoregional recurrence - Park 2017	0.519 (0.386, 0.649)	£53,554	£53,554	8.91	8.91
Distant recurrence - Park 2017	0.481 (0.351, 0.614)	£53,554	£53,554	8.91	8.91
Local/in-transit recurrence - Lee 2017	0.288 (0.175, 0.417)	£53,554	£53,554	8.91	8.91
Nodal recurrence - Lee 2017	0.192 (0.098, 0.309)	£53,554	£53,554	8.91	8.91
Systemic recurrence - Lee 2017	0.519 (0.385, 0.652)	£53,554	£53,554	8.91	8.91
Lim - Targeted therapy given BRAF positive	0.625 (0.384, 0.837)	£53,554	£53,554	8.91	8.91
Sacco - Targeted therapy given BRAF positive	0.670 (0.578, 0.756)	£53,554	£53,554	7.69	10.05
Sensitivity - NGS reference	0.859 (0.763, 0.920)	£53,554	£53,554	14.92	5.10
Specificity - NGS reference	0.955 (0.735, 0.994)	£53,554	£53,554	8.91	8.91
Stage IIC 5 year survival	0.762 (0.740, 0.783)	£53,554	£53,554	8.93	8.90
Days to COBAS result	14 (07, 21)	£53,554	£53,554	8.87	8.95
Death before IHC	0.0000 (0.0000, 0.0001)	£53,554	£53,548	8.91	8.90
IHC - total cost	£75 (£40, £200)	£18,554	£178,554	8.91	8.91
COBAS - total cost	£75 (£49, £107)	£61,121	£44,366	8.91	8.91

Table HE021: Results of the one-way deterministic sensitivity analysis – IHC & Cobas -v- Cobas alone for patients with stage III melanoma

Scenario	Base case value (range)	Incremental costs		Incremental benefits	
		Lower value	Upper value	Lower value	Upper value
Base case	-	£53,554		26.01	
Sensitivity and Specificity Standard	NGS (NGS, COBAS alone)	£53,554	£48,019	26.01	29.27
Risk of bias	All studies (All studies, Excluding high risk)	£53,554	£52,291	26.01	26.99
Targeted therapy source	Sacco (Sacco, Lim)	£53,554	£53,554	26.01	24.27
BRAF positivity rate	0.340 (0.339, 0.341)	£53,608	£53,500	25.94	26.09
Lim - Targeted therapy given BRAF positive	0.625 (0.384, 0.837)	£53,554	£53,554	26.01	26.01
Sacco - Targeted therapy given BRAF positive	0.670 (0.578, 0.756)	£53,554	£53,554	22.44	29.35
Sensitivity - NGS reference	0.859 (0.763, 0.920)	£53,554	£53,554	43.47	14.92
Specificity - NGS reference	0.955 (0.735, 0.994)	£53,554	£53,554	26.01	26.01
Stage III 5 year survival	0.762 (0.740, 0.783)	£53,554	£53,554	26.05	25.98
Days to COBAS result	14 (07, 21)	£53,554	£53,554	25.85	26.18
Death before IHC	0.0000 (0.0000, 0.0001)	£53,554	£53,548	26.01	25.99
IHC - total cost	£75 (£40, £200)	£18,554	£178,554	26.01	26.01
COBAS - total cost	£75 (£49, £107)	£61,121	£44,366	26.01	26.01

HE2.1.4.2 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (Figure HE004 and

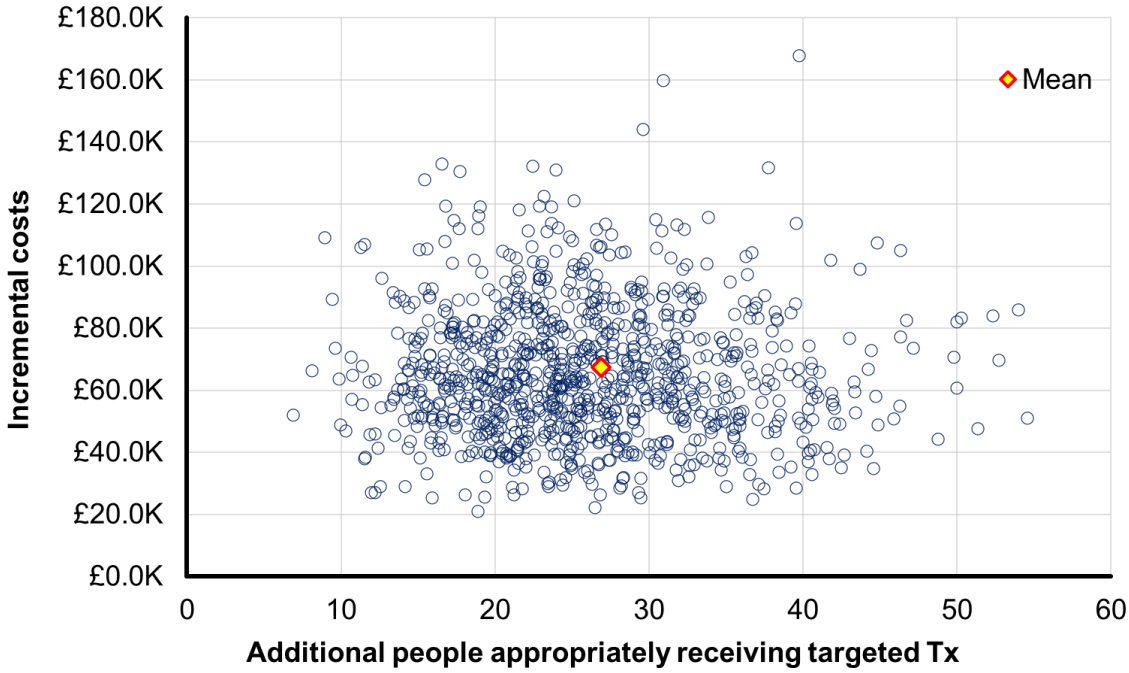


Figure **HE005** – note the scales are unique) provides additional support for the above results. For those with stage IIC and III melanoma, all iterations of the model result in an increased number of people appropriately receiving targeted therapy and increased costs when comparing IHC & PCR Cobas with PCR Cobas alone. A notable difference between the two figures is the number of people who appropriately receive targeted therapy. As discussed above, more patients with stage III melanoma go on to appropriately receive targeted therapy as a result of stage III patients being immediately eligible for targeted therapy.

Figure HE004: Probabilistic scatterplot – IHC & Cobas -v- Cobas alone for patients with stage IIC melanoma (outcomes per 1000 tested)

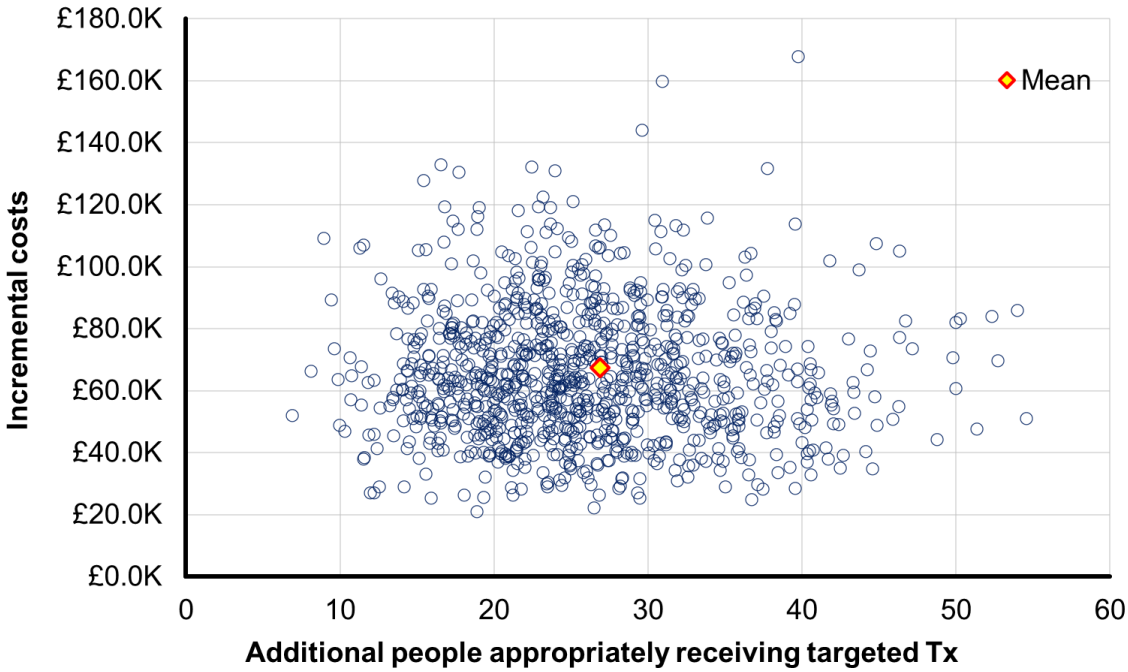


Figure HE005: Probabilistic scatterplot – IHC & Cobas -v- Cobas alone for patients with stage III melanoma (outcomes per 1000 tested)

HE2.2 Discussion

HE2.2.1 Principal findings

In the base case of the model, for both stage IIC and III melanoma, IHC & PCR Cobas results in a greater number of people appropriately receiving targeted therapy. However, this outcome is achieved at higher cost. In both stage IIC and III melanoma, the costs of each testing approach are the same, but the difference in outcomes between the two populations occurs as a result of different treatment pathways. Those with stage IIC melanoma are only eligible for targeted therapy on recurrence, whereas those with stage III melanoma are immediately eligible for targeted therapy at diagnosis after testing positive for a BRAF V600 mutation. However, the committee noted that trials are currently ongoing in which patients with stage IIC melanoma are eligible to receive adjuvant therapy at diagnosis. If the results of the trials change clinical practice the decision tree for stage IIC patients would be the exact same as the decision tree for stage III patients as both groups would be immediately eligible for targeted therapy at diagnosis. Therefore, it is likely that the testing approach of using IHC & PCR Cobas in patients with stage IIC melanoma will become more cost-effective in the future.

In sensitivity analysis, the total cost of IHC was by far the greatest contributor to model uncertainty. However, the committee felt confident in their recommendations based on both the strength of the evidence they were presented and potential future changes that may occur in clinical practice and to the cost associated with IHC testing. In our model, £200 is the upper limit to what the committee believed IHC will cost. In the committee discussions,

this £200 figure also included first year validation costs of IHC that would not be included in future years. As such, if the validation costs of IHC were distributed evenly across a longer time period, the cost of IHC would actually be less than £200. Furthermore, the committee noted how the Roche antibody for BRAF IHC testing is due to come off license, which in turn would likely result in a decrease in the cost of IHC testing as less expensive generic versions of the antibody may become available. And as noted already, the treatment pathway for stage IIC melanoma may also change in the future, resulting in more stage IIC patients going on to appropriately receive targeted therapy.

As seen in Table HE019, the total costs for each testing approach were the same regardless of the population that was modelled (i.e., stage IIC or stage III melanoma), however, in comparing the two testing approaches IHC & PCR Cobas is associated with higher costs than Cobas alone. IHC & PCR Cobas is associated with higher costs because a significant proportion of this cohort will receive two genetic tests, and receiving two genetic tests is more expensive than receiving one. All patients in this approach received an IHC test, and anyone who tested negative with IHC went on to also receive a Cobas test. The model predicted that approximately 70% of our cohort would go on to receive a Cobas test after an IHC test. There are, however, two things that could lower this number. First, the prevalence of the BRAF mutation in our populations. Our model relies on data from a UK retrospective audit in which the prevalence of the BRAF mutation in melanoma patients was approximately 34%. Other papers have estimated this figure to be as high as 50%. If the true prevalence of the BRAF mutation in our populations was higher than 34%, this would ultimately result in fewer patients receiving two tests, as fewer patients would test negative with IHC and thus fewer patients would subsequently receive a Cobas test. Second, if the sensitivity and specificities values of IHC were higher, this could also affect the number of patients who receive a second test. The sensitivity and specificities values used in the model were synthesized as part of the clinical review and were based on the best available evidence, although we were not able to determine the accuracy of a Cobas test conditional on a negative IHC test.

An additional benefit with IHC & PCR Cobas testing approach is that the majority of patients who go on to appropriately receive targeted therapy are able to begin treatment without delay. Testing with IHC has a shorter test turnaround time compared with PCR Cobas. Patients undergoing testing with IHC find out their BRAF status in a day or two (the test turnaround time for IHC) compared with 7-14 days (the test turnaround time for PCR Cobas). Ultimately, knowing one's BRAF status sooner means that one can commence targeted therapy sooner, which may be associated with additional clinical benefit to the patient.

A finding from our model was the increased number of false positives (an absolute increase of approximately 1.3%) that occur with IHC & PCR Cobas as the testing approach, as a result of the lower sensitivity of this approach compared with PCR Cobas alone. The committee considered that in practice, false positive results were unlikely to occur, and would be as a result of human error in the interpretation or in the processing of the sample. An increase in false positives should be interpreted as a potential harm, as it means that these patients will receive targeted treatment instead of a more suitable therapy, such as adjuvant pembrolizumab or other immunotherapies. These patients will not respond to targeted treatment since they do not possess the BRAF mutation, and this would be detected by their first scan at three months after starting treatment, which would likely show progression, or sooner if they deteriorated clinically during this time. These patients therefore will switch to another treatment, but there may be a proportion of patients who would no longer be eligible or sufficiently well enough to continue to receive active therapy, and there may also be some patients who would have a lower performance status who generally do less well on treatment. In contrast, a IHC & PCR Cobas strategy was associated with a lower rate of false negatives. Patients with an undetected BRAF mutation would be expected to receive a systemic therapy such as pembrolizumab. There is no direct evidence between targeted therapies and other available adjuvant therapies, but results from individual trials suggests a greater treatment effect on the rate of relapse and overall survival for dabrafenib+trametinib compared with pembrolizumab. The reduced level of treatment effectiveness will not only

have an impact of patients' health, but may also result in an increase in costs, in terms of additional outpatient attendances and treatment costs. However, the committee felt that the increased true positives and the decreased false negatives would offset the comparatively small increase in false positives and any impact that it would have on health outcomes and costs.

HE2.2.2 Strengths

This is the first economic analysis of this decision problem. Its development was informed by a multidisciplinary committee of clinical and patient experts who advised on the model structures, assumptions and potential data sources, and provided validation of the model outputs. Diagnostic accuracy was drawn from the associated clinical search. The models were able to explore a number of scenarios, reflecting the impact of a lower cost for IHC testing and a change to the stage IIC pathway whereby patients would be immediately eligible for targeted therapy at diagnosis.

HE2.2.3 Weaknesses of the analysis

The cost of each genetic test is one of the main components of our model. The model relies on data from a Dutch study (Pasmanes et al. 2019) to estimate the equipment costs for IHC and Cobas, the consumable costs for Cobas and the staff time for Cobas. Ideally, we would have preferred a data source from the UK, as it is possible that the costs in the Netherlands are different. However, no such data exist, and the committee agreed that using data from the Netherlands was a reasonable extrapolation and that it was consistent with costs applied in previous technology appraisals (TA406).

Additionally, to obtain the cost of consumables for IHC we rely on committee input in conjunction with a UK micro-costing of endometrial cancer. It would have been preferable to have a detailed list of the consumables required for BRAF V600E IHC testing, however no such list was readily available. Additionally, even if such a list was available, the primary antibodies required are still on license from Roche and are therefore unlikely to have publicly available costs. However, even at the maximum value for the cost of IHC, the ICER value for IHC & PCR Cobas was still at approximately £20,000. As discussed already, the committee felt confident this value was likely to come down in the future, both because the high cost incorporated validation costs that would only be considered in the first year thereby resulting in a lower total cost for IHC in subsequent years, and also because the Roche antibody for IHC testing will come off license and thus a further reduction in IHC tests is expected. Additionally, the committee noted studies are ongoing for stage IIC patients to receive adjuvant treatment immediately, in which case the stage IIC population would have a simplified decision tree mirroring stage III patient, both in format and in the context of model results.

The sensitivity and specificity of COBAS conditional on a negative IHC test were assumed to be the same as the sensitivity and specificity of COBAS as a first line test. This may not be an accurate assumption, given that evidence in Evidence Review A found that IHC and COBAS results are heavily correlated, and so it would not provide as much value as a second line test as would be implied by assuming independence. However, we were unable to estimate the sensitivity and specificity of COBAS as a second line test as this data were not available, and the resulting uncertainty in the analysis was reflected in the strength of the committee's recommendations for the use of front line IHC.

A further limitation is that we did not perform a cost-utility analysis, as no QALYs were estimated. The testing approaches themselves are unlikely to directly result in differences in QALYs; however, there may be downstream consequences from delivering targeted treatment to more people who are eligible. There is no head-to-head clinical or cost-effectiveness evidence for targeted treatments compared with non-targeted treatment in the adjuvant setting, and so we were unable to include QALYs in our model without conducting

an indirect analysis between all treatments and extending the modelling of benefits to capture these long-term outcomes, which was beyond the scope of this review question. Future models may expand upon our analysis by estimating QALYs that would be incurred once patients receive the treatments selected for them based on the testing results.

HE2.2.4 Comparison with other published economic analyses

Our systematic review of publishes economic analyses identified no studies of relevance to this question.

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