British Thoracic Society

NICE National Institute for Health and Care Excellence

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Draft for Consultation

Asthma: diagnosis, monitoring and chronic asthma management (update)

Cost-utility analysis: Most cost-effective sequence or combination of tests to diagnose asthma

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Economic analysis report

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1 Introduction

Asthma is one of the most common chronic diseases diagnosed in adults and children. Recent data(British Lung Foundation) suggest that around 8 million of people, 12% of the British population, have been diagnosed with asthma in the UK. However, it is widely acknowledged that not all of them genuinely have the condition as asthma tend to be overdiagnoses(Shaw, et al., 2012). The most recent figures(Asthma and Lung UK, 2023) suggest that the annual NHS cost of asthma reached £1.3 billion in 2023. Consequently, the committee recognised asthma diagnosis as a fundamental area to prioritise for economic modelling, as any improvements in diagnostic efficiency would reduce overtreatment generating NHS savings that can be reinvested in the healthcare system.

Currently, there is no gold standard test to confirm or refute asthma and current practice in the UK is heterogenous, based on clinical diagnosis of symptoms and, when available, one or more objective tests. “Trial of treatment” is also commonly used for diagnosis, where people with symptoms are started on an inhaled corticosteroid (ICS) and diagnosis is made based on the response to the medication. The committee acknowledged that current practice is heterogenous and potentially ineffective and expressed concerns of overdiagnosis and overtreatment.

Amid similar concerns, in 2017 NICE developed a comprehensive guidance(National Institute for Health and Care Excellence, 2017) for diagnosing asthma: NG80. The recommendations emphasise the importance of objective diagnostic testing in adults and children but were not systematically implemented, in part due to the rigidity of the diagnostic algorithms produced.

Therefore, a new analysis was conducted for this update, to assess the most cost-effective diagnostic strategies in children and adults. A flexible statistical model was developed in R Studio and was designed to systematically explore numerous permutations and combinations of nine diagnostic tests. The objective of the analysis was to identify a cost-effective yet easily implementable strategy.

The analysis used individual patient data (IPD) from RADicA(NHS Health Research Authority, 2019), a study involving adults and children with symptoms of asthma in England. This allowed to incorporate correlation between tests when estimating joint sensitivity and specificity of a strategy with multiple tests. Conditional dependency was expected to be particularly important in this context as certain tests measure the same phenomenon, such as inflammation of the airways or lung function, and therefore have a high likelihood of agreement. Failure of considering diagnostic performance dependency was found to cause erroneous results and biased conclusions in previously published studies(Novielli, et al., 2013).

2 Methods

2.1 Model overview

A cost-utility analysis was undertaken where lifetime quality-adjusted life years (QALYs) and costs from a current UK NHS (English NHS setting in the base case and Scottish NHS setting in a sensitivity analysis) and personal social services perspective were considered. The analysis followed the standard assumptions of the NICE reference case for interventions with health outcomes in an NHS setting including discounting at 3.5% for costs and health effects.

2.1.1 Comparators

The model was developed to assess various sequences or combinations of diagnostic tests for asthma. Each diagnostic approach comprises three or four successive steps, in which individuals undergo single tests or combinations of tests based on the outcomes of the preceding one. Two separate analyses were developed for children and adults using diagnostic data relative to the appropriate population.

The following tests were assessed in the analysis:

1. Spirometry
2. Bronchodilator reversibility test (BDR)
3. Peak expiratory flow test (PEFv)
4. Fractional Exhaled Nitric Oxide (FeNO)
5. Skin prick test – only in children
6. IgE – only in children
7. Blood eosinophils
8. Bronchial challenge test (BCT) with mannitol
9. Bronchial challenge test (BCT) with methacholine

Numerous strategies were assessed and discussed with the committee and, ultimately, the following twenty strategies were included in the base case scenario and in this report (See Table 1 and Table 2 for adults and children, respectively). See section 2.3.2.3 for insights into the rationale behind the design of these strategies.

Table 1: Diagnostic strategies in adults

S	1st step	2nd step	3rd step	4th step
1	Blood Eosinophils	+: Diagnose asthma -: BDR	+: Diagnose asthma -: Methacholine	–
2	FeNO	+: Diagnose asthma -: BDR	+: Diagnose asthma -: Methacholine	–
3	PEFv	+: Diagnose asthma -: BDR,	+: Diagnose asthma -: Methacholine,	–
4	Blood Eosinophils & FeNO	+: Diagnose asthma -: BDR,	+: Diagnose asthma -: Methacholine	–
5	Blood Eosinophils	+: Diagnose asthma -: FeNO	+: Diagnose asthma -: BDR,	+: Diagnose asthma -: Methacholine
6	Blood Eosinophils	+: Diagnose asthma -: BDR & FeNO	+: Diagnose asthma, -: Exclude asthma, ?: PEFv	+: Diagnose asthma -: Methacholine

7	Blood Eosinophils	+: Diagnose asthma -: BDR & FeNO,	+: Diagnose asthma, -: Methacholine ?: Diagnose asthma	–
8	PEFv	+: Diagnose asthma, -: BDR & FeNO	+: Diagnose asthma, -: Methacholine ?: Diagnose asthma	–
9	BDR & FeNO	+: Diagnose asthma -: Blood Eosinophils ?: Diagnose asthma	+: Diagnose asthma -: Methacholine	–
10	Blood Eosinophils & PEFv	+: Diagnose asthma -: BDR ?: Diagnose asthma	+: Diagnose asthma -: Methacholine ?: Diagnose asthma	–

Abbreviations: BDR: bronchodilator reversibility; FeNO: Fractional exhaled nitric oxide; PEFv: Peak expiratory flow variability
Legend: +: positive result at previous step; -: negative result at previous step; ?: indeterminate result at previous step

Table 2: Diagnostic strategies in children

S	1st step	2nd step	3rd step	4th step
1	FeNO	+: Dismiss -: SPT/IgE	+: Methacholine -: Dismiss	–
2	BDR	+: Dismiss -: SPT/IgE	+: Methacholine -: Dismiss	–
3	PEFv	+: Dismiss -: SPT/IgE	+: Methacholine -: Dismiss	–
4	Blood Eosinophils	+: Dismiss -: SPT/IgE	+: Methacholine -: Dismiss	–
5	FeNO	+: Dismiss -: BDR	+: Dismiss -: SPT/IgE	+: Methacholine -: Dismiss
6	FeNO	+: Dismiss -: SPT	+: Blood eosinophils -: Dismiss	+: Dismiss -: Methacholine
7	FeNO & PEFv	+: Dismiss -: SPT	+: Methacholine -: Dismiss	–
8	FeNO & Blood Eosinophils	+: Dismiss -: SPT	+: Methacholine -: Dismiss	–
9	FeNO & BDR	+: Dismiss -: SPT/IgE	+: Methacholine -: Dismiss	–
10	PEFv	+: Dismiss -: BDR	+: Dismiss -: Methacholine	–

Abbreviations: BDR: bronchodilator reversibility; FeNO: Fractional exhaled nitric oxide; PEFv: Peak expiratory flow variability; STP = skin prick test
Legend: +: positive result at previous step; -: negative result at previous step; ?: indeterminate result at previous step

2.1.2 Population

The population of the analysis was people with respiratory symptoms consistent with asthma who are not currently receiving any regular treatment. This definition aligns with the inclusion criteria established in RADicA study, which was used to estimate the accuracy of diagnostic tests in adults. It also reflects people in the UK who lack an objective diagnosis of asthma despite having asthma-like symptoms who would be referred for an objective diagnostic test. Two separate analyses were conducted for adults and children each using inputs and assumptions appropriate to the age group.

The prevalence of asthma used in the base case analysis was obtained from RADicA study and it is expected to reflect the disease prevalence among those who are seeking primary care due to asthma-like respiratory symptoms. The committee acknowledged that patient's clinical history is particularly important and emphasized its pivotal role in determining the most appropriate diagnostic sequence. In cases where there is strong evidence pointing towards asthma, such as a history of respiratory attacks and hospitalisation episodes, the likelihood of the individual having asthma is considerably high. In such instances, a strategy that has a higher sensitivity would more likely be cost-effective. Vice versa, when the likelihood of asthma is low, strategies with a better specificity become preferable. For this reason, prevalence of asthma was varied in the scenario analyses to explore potential changes in the optimal diagnostic algorithm arising from the clinical history of people with suspected asthma (see 2.5.1).

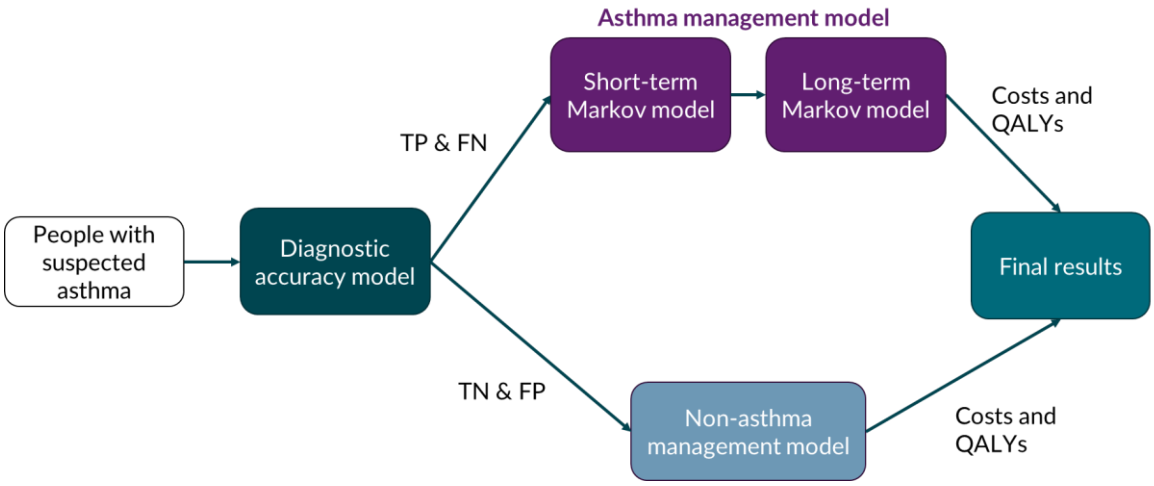
2.2 Approach to modelling

2.2.1 Model structure

The model is composed of three different sub-models (see Figure 1):

1. **The diagnostic accuracy model** is a decision tree used to determine the accuracy of the diagnostic strategies using either observed individual patient data (IPD) test results in adults from RADicA, or pseudo IPD test results in children simulated through a probit model (see 2.3.2.2). The diagnostic outcomes subsequently feed into the asthma and non-asthma management models.
2. **The asthma management model** is used to calculate costs and health outcomes of people who have asthma, distinguishing between true positive (TP) and false negative (FN). This model is divided into two Markov models for short-term and long-term.
    a. The short-term Markov model used monthly cycles to determine the duration during which individuals with asthma and a false negative diagnosis remain untreated. Once all false negative diagnoses are rectified, people enter the long-term Markov model (see also section 2.2.1.2).
    b. The long-term Markov model used yearly cycles to calculate cost and health outcomes associated with asthma throughout the cohort's lifetime (see also section 2.2.1.3).
3. **The non-asthma management model** is used to calculate costs and health outcomes of people who do not have asthma, distinguishing between true negative (TN) and false positive (FP). The model employs a partition survival approach with a fitted curve to determine the time spent with an erroneous diagnosis of asthma.

Figure 1: Model structure



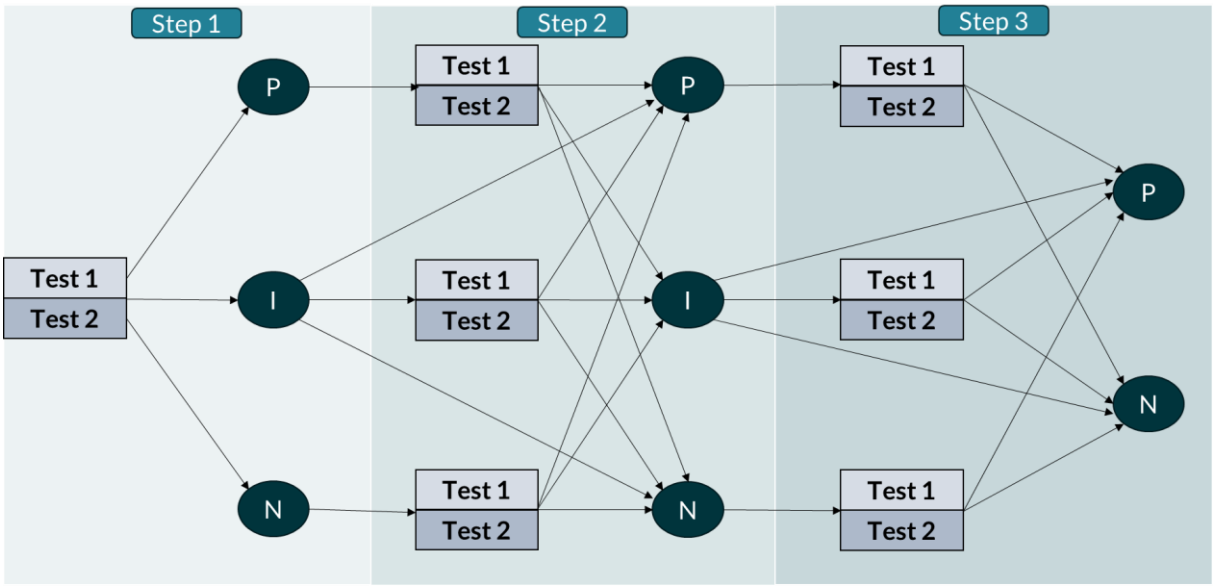
Abbreviations: TP = true positive; TN = true negative; FP = false positive; FN = false negative; QALY = Quality-adjusted life years

2.2.1.11 Diagnostic accuracy model

A decision tree was used to estimate the diagnostic accuracy of any defined strategy. Each strategy consisted of three or more sequential steps, wherein people undergo either a single test or a combination of two tests based on the outcomes of the preceding strategy (see Figure 2).

Although most of the strategies assessed have 3 steps, some with 4 steps were included too, to explore whether, although less practical, including more tests could lead to better outcomes.

Figure 2: Diagnostic sequence



Abbreviations: P: positive; I: indeterminate, N: negative.

Initially, people with respiratory symptoms suggestive of asthma are referred to the first line test or combination of tests. There are possible three outcomes after each step: positive, negative and indeterminate, with the last occurring only when two tests given together report conflicting results. In step 2 and 3, a decision is made based on results of the previous step on whether to dismiss the patient with a diagnosis (asthma or non-asthma) or offer further tests. When people receive a different outcome at a following step, the model considers only the latter one. Upon reaching the last step, people are either dismissed or received their final tests that will determine their ultimate diagnosis.

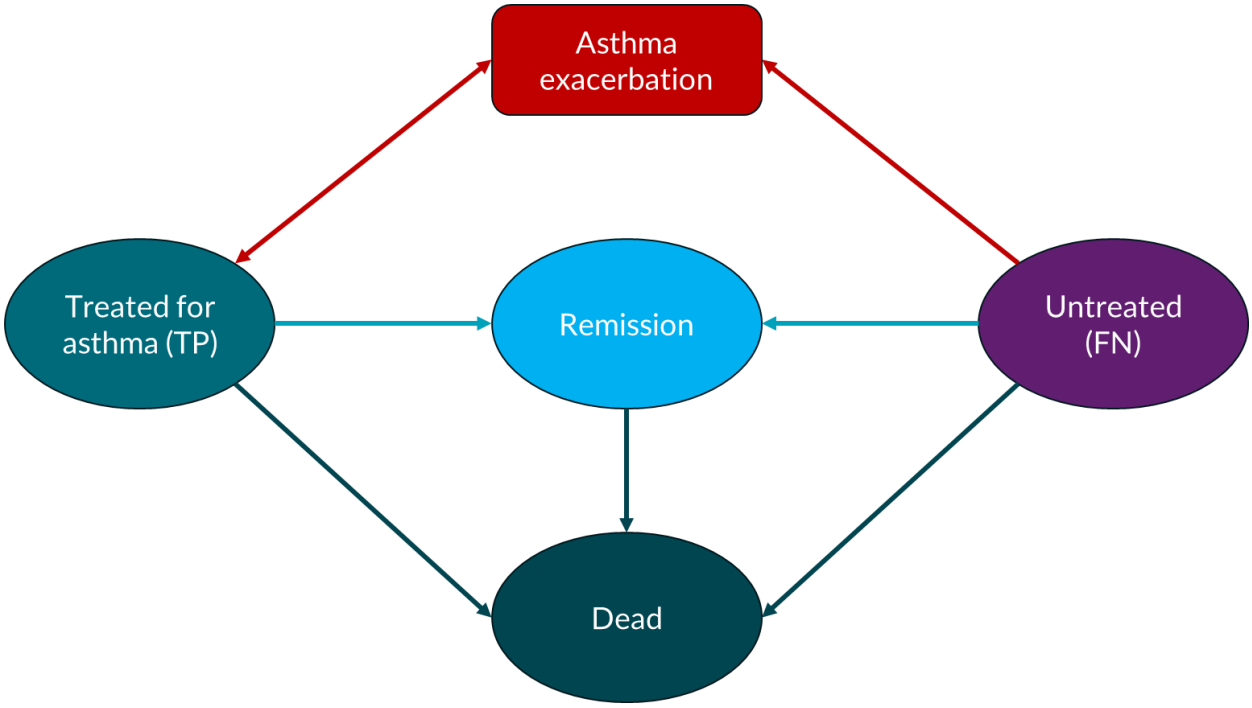
Conditional dependencies between tests in adults was naturally incorporated in this analysis as the use of individual level data from a single study allows to estimate “joint sensitivity” and “joint specificity” of any relevant diagnostic sequences (see section 2.3.2). In children this was not possible, as there was no robust IPD available. Therefore, a different approach was adopted where test results were simulated through a multivariate probit model using accuracy data from the clinical review and correlation from RADicA (see section 2.3.2.2Diagnostic accuracy in children – Multivariate Probit model).

Estimated joint sensitivity and specificity values are used to determine the number of true positive (TN), true negative (TN), false positive (FP), false negative (FN) associated with each strategy, that were subsequently fed into the two management models.

2.2.12 Asthma management model

Two different Markov models were used for people who have asthma: a short-term model (Figure 3) using monthly cycles and a long-term model (Figure 4) using yearly cycles.

Figure 3: Short-term Markov model



Abbreviations: TP: true positive; FN: false negative

People with asthma initially enter the short-term model (Figure 3) in either the "treated for asthma" (true positive) or "untreated" (false negative) states with a proportion depending on the sensitivity of the corresponding diagnostic strategy. Monthly cycles were preferred to annual cycles to adequately reflect time-to-first exacerbations in those who are untreated (see section 2.3.3.1.2).

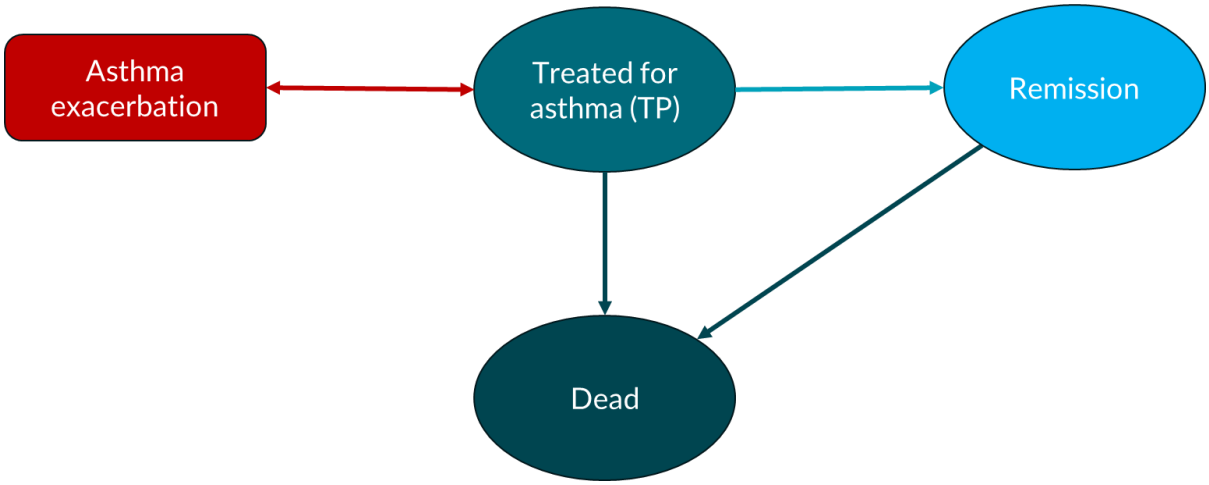
People who are treated for asthma incur monthly costs related to asthma therapy and annual costs for monitoring and have the quality of life and mortality of people with asthma. People who are untreated do not incur any cost but suffer from a lower quality of life and a slightly higher mortality due to inadequate asthma control. Remission is allowed only in those who were diagnosed with asthma during their childhood (see 2.3.3.1.3) and therefore is only incorporated into the children's model.

Both treated and untreated people face a risk of experiencing an asthma exacerbation, with a higher risk applied to those who are untreated. Once a person with untreated asthma experiences an exacerbation (either mild/moderate or severe), the model assumes that they will seek additional diagnostic advice and be referred for a bronchial challenge test with methacholine or mannitol (BCT), leading to a conclusive asthma diagnosis and their ultimate transition to the "treated for asthma" state. This was considered appropriate by the committee, as people with a history of asthma attacks but uncertain diagnosis typically undergo further diagnostic tests and receive a diagnosis based on the results and their clinical history. If the symptoms persist, a "trial of treatment" might also be considered to assess the patient's response to asthma treatment. An asthma exacerbation was not modelled as a separate Markov state, but rather as a transitory outcome occurring each cycle, which is used to estimate costs and loss of quality of life associated with the episode, and to determine the number of false negative people transitioning to the true positive state.

People in both the untreated and treated states have a monthly probability of dying which was estimated from a longitudinal population-based asthma cohort study(Lemmetyinen, et al., 2018). Those with untreated asthma have a slightly higher probability of dying from their disease. While very rare, a severe exacerbation could lead to death: however, the model does not apply a mortality effect to exacerbations to prevent double counting, given that the baseline mortality rates already include deaths attributed to asthma attacks.

After a specific period determined by the committee to be around 2 years in the base case (equivalent to 24 cycles), the model assumes that people whose asthma is still untreated will seek further medical advice and be referred for a BCT that will ultimately lead to the correct diagnosis of asthma. They will then move to the long-term Markov model (Figure 4).

Figure 4: Long-term Markov model



Abbreviation: TP: true positive

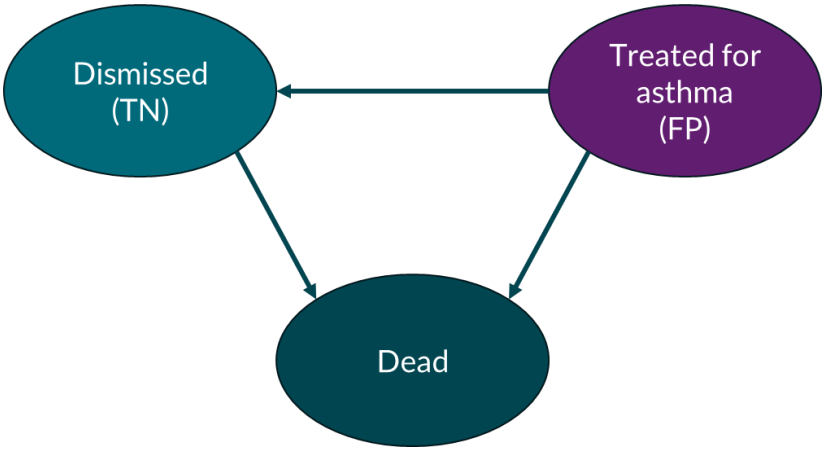
In the long-term Markov model, people start in either the “remission” or “treated for asthma” states as is assumed that any remaining false negative asthma diagnosis was corrected in the last cycle of the short-term model.

The long-term model uses annual cycles to simulate the lifetime of people until they either reach the end of their life or the age of 100. Similar to the short-term model, transitions to remission are only allowed for cohorts diagnosed with asthma during childhood.

2.2.12.3 Non-asthma management model

People who do not have asthma enter the non-asthma management model either as true negative or false positive depending on the specificity of the corresponding diagnostic strategy. The model employs a partition survival approach with three exclusive states to determine the long-term consequences associated with any diagnostic strategy (see Figure 5).

Figure 5: Negative trace – health states of the partition survival model



Abbreviations: TN: true negative; FP: true positive

People who are correctly identified as not having asthma (true negative), enter the model in the "dismissed" state, where they are assumed to receive the appropriate therapy for their underlying condition. Consequently, the model applies no extra cost, adverse impact on quality of life or excess mortality to this state.

People who are erroneously diagnosed with asthma, enter the model in the "treated for asthma" state, where they remain for a period determined by a distribution curve that was fitted to data from a Canadian longitudinal study (see section 2.2.1.3). As respiratory symptoms caused by conditions other than asthma are not expected to improve with asthma therapy, people in this state exhibit a lower quality of life than the general population throughout the duration of their misdiagnosis. A survival curve based on the general population mortality was used to determine the number of people that die each year (see limitations in section 4.2).

2.2.2 Uncertainty

The model was built probabilistically to take account of the uncertainty around input parameter point estimates. A probability distribution was defined for each model input parameter. When the model was run, a value for each input was randomly selected simultaneously from its respective probability distribution; mean costs and mean QALYs were calculated using these values. The model was run repeatedly – 10,000 times for the base case and each sensitivity analysis – and results were summarised.

The way in which distributions are defined reflects the nature of the data, so for example event probabilities were given a beta distribution, which is bounded by 0 and 1, reflecting that the probability of an event occurring cannot be less than 0 or greater than 1. All of the variables that were probabilistic in the model and their distributional parameters are detailed in Table 3 and in the relevant input summary tables in section 2.3.1. Probability distributions in the analysis were parameterised using error estimates from data sources.

Table 3: Description of the type and properties of distributions used in the probabilistic sensitivity analysis

Parameter	Type of distribution	Properties of distribution
Proportion of people receiving a test at each step Test sensitivity	Beta	Bounded between 0 and 1. As the sample size and the number of events were specified alpha and beta values were calculated as follows: • Alpha = (number of patients hospitalised)

Parameter	Type of distribution	Properties of distribution
Proportion of severe exacerbations		• Beta = (number of patients) − (number of patients hospitalised)
Annualised exacerbation rates N. of inhaler actuations per day Utility decrements	Gamma	Bounded at 0, positively skewed. Derived from mean and its standard error. Alpha and beta values were calculated as follows: • Alpha = $(mean/SE)^2$ • Beta = $SE^2/Mean$
Diagnostic odds ratio Hazard ratios Relative risks Utility multipliers Parameters of survival curves	Lognormal	The natural log of the mean and standard error were calculated as follows: • Mean = ln(mean cost) − $SE^2/2$ • SE = [ln(upper 95% CI) − ln(lower 95% CI)]/(1.96×2) $\sqrt{\ln \frac{SE^2 + mean^2}{mean^2}}$ This formula includes a correction to ensure the mean generated in the probabilistic analysis will be the same as the reported mean.

Abbreviations: 95% CI = 95% confidence interval; SE = standard error

The following variables were left deterministic (that is, they were not varied in the probabilistic analysis):

- the cost-effectiveness threshold (which was deemed to be fixed by NICE),
- the cost of staff required to administer each test (assumed to be fixed according to national pay scales)
- the time required for each test, which was informed from the committee and, when necessary, varied in the sensitivity analysis
- cost of healthcare services available in UK national sources
- drug prices
- mortality in the general population based on life tables
- utility score in the general population
- prevalence of asthma

In addition, various deterministic sensitivity analyses were undertaken to test the robustness of model assumptions. In these, one or more inputs were changed and the analysis rerun to evaluate the impact on results and whether conclusions on which intervention should be recommended would change. Details of the sensitivity analyses undertaken can be found in methods section 2.5.

2.3 Model inputs

2.3.1 Summary table of model inputs

Model inputs were based on clinical evidence identified by the committee, supplemented by additional data sources as required. Model inputs were validated with clinical members of the guideline committee. A summary of the model inputs used in the base-case (primary) analysis is provided in Table 4 below. More details about sources, calculations and rationale for selection can be found in the sections following this summary table.

Table 4: Overview of parameters and parameter distributions used in the model

Input	Data	Source	Probability distribution
Population	People with suspected asthma		n/a
Starting age	Adults: 30 Children: 12	Committee's opinion	n/a
Prevalence of asthma among those with symptoms	59%	RADicA(NHS Health Research Authority, 2019)	n/a
Perspective	UK NHS & PSS	NICE reference case	n/a
Time horizon	Lifetime		n/a
Discount rate	Costs: 3.5% Outcomes: 3.5%	NICE reference case	n/a
Test accuracy in adults			
Skin prick test	Sensitivity: 0.74 Specificity: 0.52	RADicA(NHS Health Research Authority, 2019)	Specificity: beta DOR: lognormal
BDR	Sensitivity: 0.41 Specificity: 1.00	RADicA(NHS Health Research Authority, 2019)	Specificity: beta DOR: lognormal
PEFv	Sensitivity: 0.15 Specificity: 0.97	RADicA(NHS Health Research Authority, 2019)	Specificity: beta DOR: lognormal
Blood eosinophils	Sensitivity: 0.32 Specificity: 0.98	RADicA(NHS Health Research Authority, 2019)	Specificity: beta DOR: lognormal
FeNO	≥ 50ppb Sensitivity: 0.53 Specificity: 0.87 ≥ 40ppb Sensitivity: 0.59 Specificity: 0.85	RADicA(NHS Health Research Authority, 2019)	Specificity: beta DOR: lognormal
Spirometry	Sensitivity: 0.37 Specificity: 0.96	RADicA(NHS Health Research Authority, 2019)	Specificity: beta DOR: lognormal
Mannitol challenge test	Sensitivity: 0.63 Specificity: 0.93	RADicA(NHS Health Research Authority, 2019)	Specificity: beta DOR: lognormal
Methacholine challenge test	Sensitivity: 0.62 Specificity: 1.00	RADicA(NHS Health Research Authority, 2019)	Specificity: beta DOR: lognormal
Conditional between tests	Observed in RADiCA IPD	RADicA(NHS Health Research Authority, 2019)	n/a
Test accuracy in children			
Skin prick test	Sensitivity: 0.83 Specificity: 0.72	Drkulec 2013(Drkulec, et al., 2013)	n/a
Serum total IgE	Sensitivity: 0.97 Specificity: 0.77	Drkulec 2013(Drkulec, Nogalo, Perica, Plavec, Pezer, Turkalj, 2013)	n/a

Input	Data	Source	Probability distribution
BDR	Sensitivity: 0.14 Specificity: 0.93	Murray 2017(Murray, et al., 2017)	n/a
PEFv	Sensitivity: 0.5 Specificity: 0.72	Brouwer 2010(Brouwer, et al., 2010)	n/a
Blood eosinophils	Sensitivity: 0.37 Specificity: 0.91	Livnat 2015(Livnat, et al., 2015)	n/a
FeNO	Sensitivity: 0.32 Specificity: 0.99	Woo 2012(Woo, et al., 2012)	n/a
Spirometry	Sensitivity: 0.32 Specificity: 0.99	Eom 2020(Eom, et al., 2020)	n/a
Methacholine challenge test	Sensitivity: 0.68 Specificity: 0.76	Zaczeniuk 2015(Zaczeniuk, et al., 2015)	n/a
Correlation between tests	Observed in RADiCA IPD	RADicA(NHS Health Research Authority, 2019)	n/a
Natural history			
Annualised exacerbation rates	ICS/LABA: 0.195 ICS + SABA: 0.175	Novel START(Beasley, et al., 2019)	Gamma
Time-to-first exacerbation (exponential)	λ = 0.000855	Estimated using pseudo-IPD from Novel START(Beasley, Holliday, Reddel, Braithwaite, Ebmeier, Hancox, Harrison, Houghton, Oldfield, Papi, Pavord, Williams, Weatherall, Novel, 2019)	Lognormal
Proportion of severe exacerbations	ICS/LABA = 0.24 SABA (untreated) = 0.31	Novel START(Beasley, Holliday, Reddel, Braithwaite, Ebmeier, Hancox, Harrison, Houghton, Oldfield, Papi, Pavord, Williams, Weatherall, Novel, 2019)	Beta
Time-to-remission (lognormal)	**Age 0 – 5** Mean = 2.15 SD = 1.67 **Age 5 –10** Mean = 2.62 SD = 1.77 **Age 10 – 15** Mean = 3.36 SD = 2.01	Estimated using pseudo-IPD from De Marco 2002(De Marco, et al., 2002)	Lognormal
Time-to-FP diagnosis correction (Weibull)	Shape = 1.11 Scale = 0.37	Estimated from Pakhale 2011(Pakhale, et al., 2011)	Multivariate lognormal
Incident rate ratios (IRR) for exacerbation	Infant vs adults = 1.33 Children vs adults = 0.46	Estimated from Bloom 2018(Chloe, et al., 2018)	Lognormal

Input	Data	Source	Probability distribution
Median time to first exacerbation	Infant (0 – 4) = 2.83 years Children (5 – 17) = 8.5 years Adults (18 – 55) = 3.5 years	Bloom 2018(Chloe, Francis, Ian, Liam, Paul, Jennifer, 2018)	N/A
Mortality			
General population mortality	Age- and gender specific	ONS Life tables 2018-2020(Office for National Statistics, 2021)	Fixed
People with asthma	**Adults:** HR = 1.25 **Children** HR = 1.77	Lemmetyinen 2018(Lemmetyinen, Karjalainen, But, Renkonen, Pekkanen, Toppila-Salmi, Haukka, 2018) Fleming 2019(Fleming, et al., 2019)	Lognormal
Asthma CFR	0.0002288889	ONS death registration 2022(Office for National Statistics, 2023)	Fixed
Asthma mortality if untreated	RR = 2	Suissa 2000(Suissa, et al., 2000)	Fixed
Health-related quality of life (utilities)			
General population utilities	Age- and gender specific	NICE Decision Support Unit(Alava, et al., 2022)	Fixed
Utility multiplier – people on asthma treatment	0.892	Health Survey for England 2018(NHS Digital, 2019)	Gamma of the difference
Utility multiplier – people with uncontrolled asthma	0.845	Health Survey for England 2018(NHS Digital, 2019)	Gamma of the difference
Utility multiplier – people in remission	0.989	Health Survey for England 2018(NHS Digital, 2019)	Lognormal
Utility value - children	0.96	Kua 2016(Kua, et al., 2016)	Beta
Utility decrements with moderate exacerbations	7 days = 0.0921 14 days = 0.0876 21 days = 0.0867 28 days = 0.0834	Briggs 2021(Briggs, et al., 2021)	Gamma
Utility decrements with severe exacerbations	7 days = 0.163 14 days = 0.132 21 days = 0.125 28 days = 0.115	Briggs 2021(Briggs, Nasser, Hammerby, Buchs, Virchow, 2021)	Gamma
Costs			
GP visit	£38	PSSRU 2022(Jones, et al.)	Fixed
Practice nurse visit	£16.39	PSSRU 2022(Jones, Birch, Dargan, Forder, Roland)	Fixed

Input	Data	Source	Probability distribution
Outpatient visit	Adults: £185 Children: £266	National Cost Collection 2021/22(NHS England, 2022)	Fixed
Consultant-led visit	Adults: £194 Children: £301	National Cost Collection 2021/22(NHS England, 2022)	Fixed
GP per hour	£244	PSSRU 2022(Jones, Birch, Dargan, Forder, Roland) NHS Supply Chain Catalogues(NHS Supply Chain Catalogue., 2022) Committee's expert opinion	Fixed
Nurse per hour	£63.38		Fixed
Spirometry	£22.93		Fixed
BDR	£39.16		Fixed
PEFv	£25.78		Fixed
FeNO	£22.21		Fixed
Skin prick test	£44.58		Fixed
Total serum IgE	£16.03		Fixed
Blood eosinophils	£7.66		Fixed
Bronchial challenge test with methacholine or mannitol	£179.49		Fixed
Actuations per day – ICS/LABA	Budesonide formoterol = 0.53	Novel START(Beasley, Holliday, Reddel, Braithwaite, Ebmeier, Hancox, Harrison, Houghton, Oldfield, Papi, Pavord, Williams, Weatherall, Novel, 2019)	Gamma
Actuations per day – ICS+SABA	Budesonide = 1.11 Albuterol = 1.01	Novel START(Beasley, Holliday, Reddel, Braithwaite, Ebmeier, Hancox, Harrison, Houghton, Oldfield, Papi, Pavord, Williams, Weatherall, Novel, 2019)	Gamma
ICS cost per inhaler	Budesonide inhaler = £14.25	BNF 2024(Joint Formulary Committee, 2024)	Fixed
SABA cost per inhaler	Albuterol inhaler = £1.50	BNF 2024(Joint Formulary Committee, 2024)	Fixed
ICS/LABA cost per inhaler	Budesonide formoterol inhaler = £28	BNF 2024(Joint Formulary Committee, 2024)	Fixed
Cost of monitoring asthma	Without FeNO = £58.54 With FeNO = £62.53	PSSRU 2022(Jones, Birch, Dargan, Forder, Roland) Committee's expert opinion	Fixed
Cost of a mild/moderate exacerbation	£42	PSSRU 2022(Jones, Birch, Dargan, Forder, Roland) BNF(Joint Formulary Committee, 2024)	Fixed

Input	Data	Source	Probability distribution
		NHS Supply Chain Catalogues(NHS Supply Chain Catalogue., 2022)	
Severe exacerbation	Proportion requiring SGC = 80% Proportion requiring A&E = 13% Proportion requiring hospitalisation = 7%	Sygma 2(Bateman, et al., 2018)	Dirichlet
Cost of SGC therapy	Adults = £1.88 [b] Children = £0.60 [c]	BNF 2024(Joint Formulary Committee, 2024)	
Cost of A&E visit	£113	National Cost Collection 2021/22(NHS England, 2022)	Fixed
Cost of asthma hospitalisation	Adults: £1,181 Children: £1,223	National Cost Collection 2021/22(NHS England, 2022)	Fixed

Abbreviations: A&E = accident and emergency; CFR = Case fatality rate; SGC = systemic glucocorticoids
a) 8 tablets of prednisolone 5mg a day for 7 days
b) 6 tables of prednisolone 5 mg a day for 3 days

2.3.2 Accuracy analysis

When estimating joint sensitivity and joint specificity of a sequence of tests, it is important to incorporate conditional dependencies. For instance, two tests that measure the same phenomenon, like inflammation of the lungs, are more likely to give the same result, and therefore less useful to be administered together. Novielli and colleagues conducted an analysis on the accuracy of Wells score and Ddimer in combination and found that failing to account for diagnostic performance dependency led to erroneous results and biased conclusions(Novielli, Cooper, Sutton, 2013). This model incorporates conditional dependency using two different approaches in adults and children.

In adults, joint sensitivity and joint specificity of all strategies were calculated directly from a relevant individual patient data (IPD) study(NHS Health Research Authority, 2019), which was recently conducted in the UK. This approach allowed to incorporate conditional dependencies as information was available on the results of multiple tests for each individual. Nevertheless, this approach might also introduce biases if factors such as a small sample size or improper inclusion/exclusion criteria lead to the inaccurate estimation of the accuracy of one or more tests. Further discussion on this can be found in the limitations section (see 4.2).

In children, no IPD study including all the relevant tests was identified, so the same approach could not be adopted. Instead, data from the clinical review were combined with the correlation matrix estimated in RADicA to generate pseudo IPD. These simulated IPD were then used to estimate joint sensitivity and specificity.

Prevalence of asthma among those with respiratory symptoms, was estimated using RADicA study on adults: 59%. No source was identified for children so the same prevalence was used. However, sensitivity analyses were carried out in both populations adjusting for scenarios of reduced and increased prevalence.

2.3.2.11 Diagnostic accuracy in adults – RADicA IPD

Diagnostic accuracy data in adults is sourced from the Rapid Access Diagnostics for Asthma (RADicA), a prospective observational study involving adults and children with symptoms consistent with asthma(NHS Health Research Authority, 2019). Participants underwent both standard and novel lung function tests, as well as blood and skin prick tests, before receiving their final diagnosis. Confidential academic data from a sample of 118 adults in this study was analysed to estimate the accuracy of several potential diagnostic combination. See Evidence Review K for more details.

Table 5 illustrates the accuracy of each test included in RADicA alongside the criteria for positivity used in the study. For FeNO, two different criteria for positivity were tested: ≥ 40ppb and ≥ 50ppb.

Table 5: Diagnostic accuracy of tests in adults

Test	Criteria for positivity	Sensitivity	Specificity
Skin prick test	any positive SPT to 8 common inhaled allergens.	0.74 (0.63 – 0.83)	0.52 (0.38 – 0.66)
BDR	≥ 12% + at least 200ml	0.41 (0.31 – 0.53)	1.00 (0.93 – 1.00)
PEFv	"[(higher-lower)/mean]*100" per day average over AT LEAST 5 days	0.15 (0.08 – 0.27)	0.97 (0.86 – 0.99)
Blood eosinophils	>0.4x10^9 cells/L	0.32 (0.22 – 0.44)	0.98 (0.89 – 0.99)
FeNO	≥ 50ppb	0.53 (0.41 – 0.64)	0.87 (0.75 – 0.94)
FeNO	≥ 40ppb	0.59 (0.47 – 0.69)	0.85 (0.73 – 0.93)
Spirometry	FEV1/FVC < LLN	0.37 (0.27 – 0.49)	0.96 (0.86 – 0.99)
Mannitol challenge test	PD15 ≤ 635mg	0.63 (0.45 – 0.78)	0.93 (0.79 – 0.98)
Methacholine challenge test	PD20 < 200mcg	0.62 (0.49 – 0.74)	1 (0.92 – 1.00)

Abbreviations: BDR: bronchodilator reversibility; FeNO: Fractional exhaled nitric oxide; PEFv: Peak expiratory flow variability; SPT: skin prick test.
Source: RADicA(NHS Health Research Authority, 2019)

As anticipated, many asthma tests exhibit high specificity, especially PEFv, BDR, spirometry, blood eosinophils, and the two bronchial challenge tests. However, sensitivity tends to be modest for most tests, except for the two bronchial challenge tests and skin prick test. These values align generally well with the accuracy found in the clinical review with a few exceptions:

1. BDR was found to be very specific in the clinical review but with a value below 0.9. A similar sensitivity of 0.41 was estimated in a study which used a slightly different criteria for positivity: ≥15% and/or at least 200ml
2. Likewise, studies included in the literature review on blood eosinophils generally report a high specificity but inferior to 0.9 at different thresholds
3. There was some uncertainty on the specificity value of FeNO in the clinical review. A few studies(Kowal, et al., 2009, Schneider, et al., 2022) on adults using a cut-off value of 50 ppb found a higher specificity (between 0.91 and 0.99) than the estimation from RADicA. This prompted to conduct a threshold analysis on the specificity of FeNO (see section 2.5.2).
4. Bronchial challenge test with methacholine generally showed a higher sensitivity but worse specificity in the clinical review although no study using the same threshold was included.

This and other limitations associated with using IPD from RADicA to estimate diagnostic accuracy are further discussed in the limitations section (see section 4.2).

As conditional dependency between tests is a crucial aspect of this analysis, correlation between tests was explored using the Psych package of R studio. Polychoric correlation coefficients were calculated with bootstrapped confidence intervals (see Table 6, Figure 6 and Figure 7). Polychoric correlations were preferred to other correlation measures, such as Pearson's coefficients, as these are most appropriate for tests defined by cut-points on an underlying continuous scale, assumed to be normally distributed for each test.

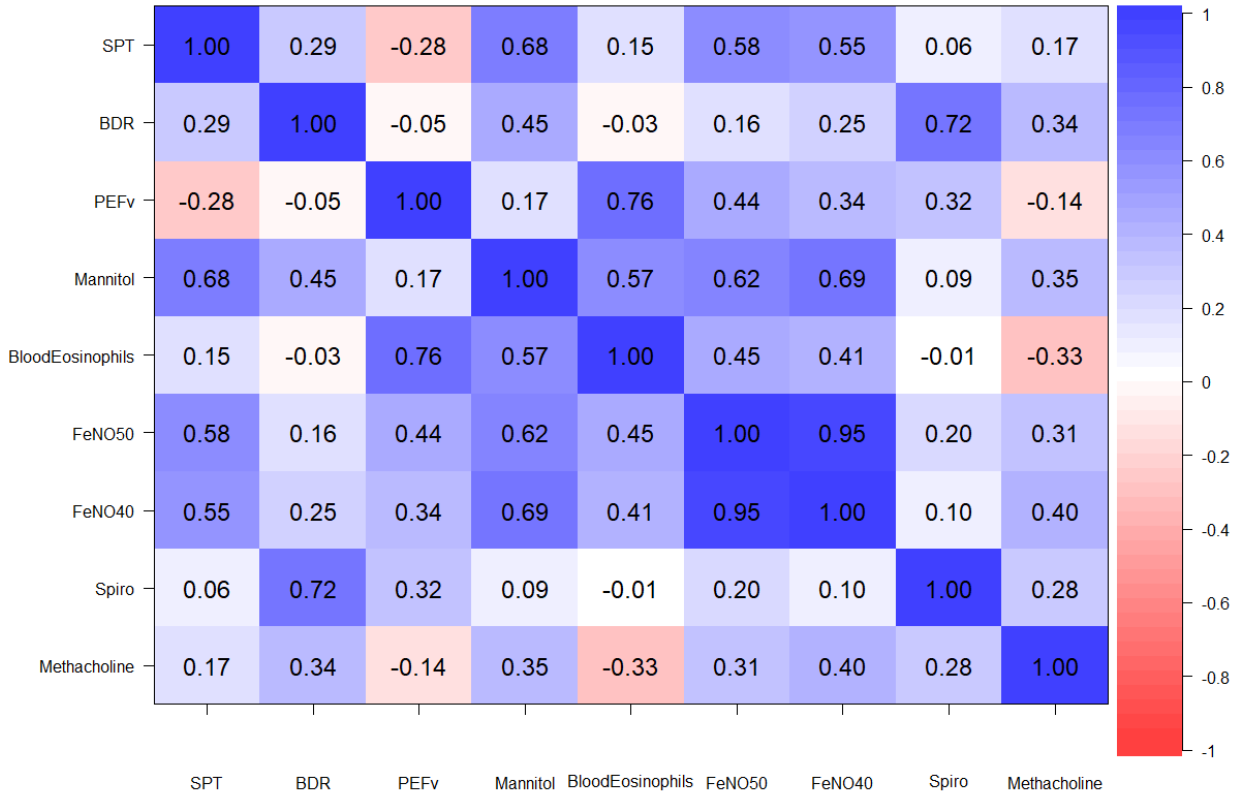
A value of 1 indicates perfect correlation, which occurs when two tests consistently give the same results. A value of 0, instead, indicates perfect independence. Independent tests are more likely to be useful when given in a sequence, as independent tests can potentially rectify errors made by each other.

Table 6: Correlation between tests results – people with asthma

	SPT	BDR	PEFv	Mannitol	Blood Eosinophils	FeNO 50	FeNO 40	Spiro	Methacholine
SPT	1								
BDR	0.29	1							
PEFv	-0.28	-0.05	1						
Mannitol	**0.68****	0.45	**0.17*****	1					
Blood Eosinophils	0.15	-0.03	**0.76*****	**0.57*****	1				
FeNO 50	**0.58*****	0.16	0.44	**0.62****	0.45	1			
FeNO 40	**0.55*****	0.25	0.34	**0.69***	0.41	**0.95*****	1		
Spiro	0.06	**0.72*****	0.32	0.09	-0.01	0.20	0.10	1	
Methacholine	0.17	0.34	-0.14	0.35	-0.33	0.31	**0.40***	0.28	1

*Note: *** ρ < 0.001, ** ρ < 0.01, * ρ < 0.05*
Abbreviations: BDR: bronchodilator reversibility; FeNO: Fractional exhaled nitric oxide; PEFv: Peak expiratory flow variability; STP = skin prick test

Figure 6: Correlation plot – people with asthma



Abbreviations: BDR: bronchodilator reversibility; FeNO: Fractional exhaled nitric oxide; PEFv: Peak expiratory flow variability; STP = skin prick test

Figure 7: Correlation plot – people without asthma

Abbreviations: FeNO: Fractional exhaled nitric oxide; PEFv: Peak expiratory flow variability; STP = skin prick test;
Note: tests with perfect specificity were removed from the plot

The Polychoric correlation coefficients reported in Table 6 aligned well with committee's expectations. As anticipated, BDR and spirometry were found to be significantly correlated, as both measure airway obstruction. Blood eosinophils was found to be moderately correlated with FeNO. This was also expected as these tests generally capture markers of inflammation rather than markers of airflow obstruction. Noticeably, PEFv and blood eosinophils were found to be significantly correlated with a Polychoric coefficient of 0.76. The strong correlation between these two poorly sensitive tests could be explained by the fact that both somehow identify those with severe asthma but fail to recognize milder manifestations of the disease. This is also likely to be the reason behind the observed correlations between skin prick test, mannitol and FeNO.

Challenge test with methacholine was found to be only weakly correlated only with FeNO (40pp). This was somewhat expected as bronchial challenge tests are typically assumed to be independent of most other available tests. However, it is noteworthy that the lack of correlation between the methacholine and mannitol challenge tests is somewhat unusual. Contrary findings were reported by Porbodis and colleagues(Porpodis, et al., 2017), who observed a significant and robust correlation between the two tests (Person's r = 0.93 ρ < 0.001). In the context of RADicA study, the more likely explanation is the large number of missing values of mannitol, as this test was only optional and available after receiving a mandatory methacholine test. As the large number of missing values with mannitol might introduce biases in diagnostic strategies that includes this test, a pragmatic choice was made to consider methacholine as the standard bronchial challenge test. This is not expected to introduce significant biases as methacholine reflects current practice for bronchial challenge tests. Moreover, when analyses were run using mannitol instead of methacholine, there was no difference in the relative cost-effectiveness of the strategies analysed.

2.3.2.2 Diagnostic accuracy in children – Multivariate Probit model

While in adults IPD from a single study including all relevant tests was used, there was no similar study on children. Therefore, a different approach was employed. Sensitivity and specificity of each test were estimated from the studies included in the clinical review that were deemed most appropriate by the committee and representative to the UK in terms of population and criteria for positivity (see Table 7). The only exception was BDR as no study was included in children, so data from Murray 2017(Murray, Foden, Lowe, Durrington, Custovic, Simpson, 2017) was used, despite its exclusion due to the reference standard not including an objective test or clinical diagnoses but being based on an established epidemiological 3-question form. Further details on these limitations, including the quality of some the studies, are discussed in the limitations section (see section 4.2).

Table 7: Accuracy of diagnostic tests in children

Test	Criteria for positivity	Sensitivity	Specificity	Source and population	Quality
Skin prick test	House dust mite > 3mm	0.83	0.72	Druklec 2013 (Children 1 – 15)	Very low Very low
IgE	Cut-off: >116.6 kIU/L	0.97	0.77	Druklec 2013 (Children 1 – 15)	Very low Very low
BDR	≥ 12% + at least 200ml	0.14	0.93	MAAS Murray 2017 (Children 12 – 16)	- -
PEFv	Mean peak expiratory flow variability ≥12.3% over 14 days	0.50	0.72	Brower 2010 (Children 6 – 16)	High Moderate

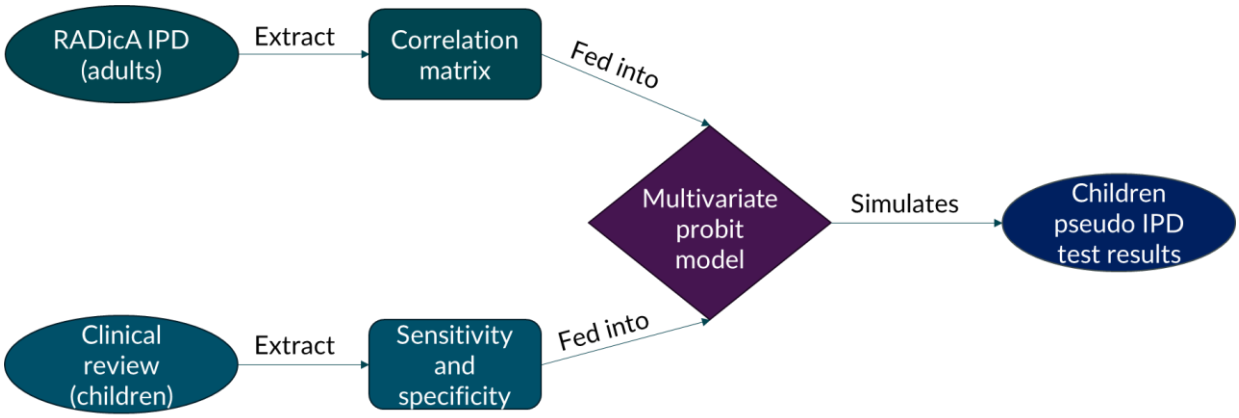
Test	Criteria for positivity	Sensitivity	Specificity	Source and population	Quality
Blood eosinophils	cut-off: 500/mL	0.37	0.91	Livnat 2015 (Children 6 – 18)	Low Very low
FeNO	≥ 35 ppb	0.32	0.99	Woo 2012 (Children 8 – 16)	High High
Spirometry	Predicted FEV1 (cut-off: 88.4%)	0.68	0.76	Eom 2020 (Children 8 – 16)	Moderate Low
Methacholine challenge test	PD20 FEV1 ≤0.72 mg	0.9	0.82	Zaczeniuk 2015 (Children 10 – 18)	Very low Very low

Abbreviations: BDR: bronchodilator reversibility; FeNO: Fractional exhaled nitric oxide; PEFv: Peak expiratory flow variability; STP = skin prick test

As no study on correlation between tests in children was identified, it was assumed that the same correlation observed in adults from RADicA would apply to children. This was considered appropriate by the committee as correlation between two test results typically stems from the tests measuring similar phenomena, such as lung capacity or inflammation. The age of the patients, on the other hand, is not expected to significantly affect conditional dependency.

Diagnostic accuracy from Table 7 and correlations between tests from Table 6 were combined to generate pseudo test results in children through a multivariate probit model as shown in Figure 8.

Figure 8: Generating pseudo IPD test results in children



A multivariate probit model is a generalisation of the probit model that allows to estimate several correlated binary outcomes jointly. This is appropriate to model outcomes that are expected to affect each other, such as the probability that a range of tests would give a positive or negative result(Chib, et al., 1998). In a normal probit there is only one dependent variable Y and a latent variable Y*. In contrast, in a multivariate probit model, there are n dependent and latent variable that are correlated with each other. Dependent variables assume the value of 1 (positive test result) when the underlying continuous latent variable is positive, and vice versa the value of 0 when the latent variable is negative:

$$Y_1 = \begin{cases} 1 \; if \; Y_1^* > 0, \\ 0 \; if \; Y_1^* < 0 \end{cases}$$

$$Y_2 = \begin{cases} 1 \; if \; Y_2^* > 0, \\ 0 \; if \; Y_2^* < 0 \end{cases}$$

...

$$Y_n = \begin{cases} 1 \; if \; Y_n^* > 0, \\ 0 \; if \; Y_n^* < 0 \end{cases}$$

with each latent variable Y* dependent on a parameter β, and a correlation matrix ρ. The parameter β was calculated by transforming sensitivity and specificity values of each test into "probability unites" (probit) and assuming they are normally distributed across the simulated population. Values for the correlation matrix ρ were taken from Table 6. Tests with a correlation below 0 were considered perfectly independent, as negative values were likely caused by the small sample of the study. For tests whose correlations among people without asthma could not be estimated, BDR and methacholine, a pragmatic choice to use the same correlation observed among those with asthma was made.

Using the multivariate probit described above, 10,000 pseudo IPD test results were generated for children with asthma and children without asthma. These pseudo IPD test results reflect the accuracy observed in the clinical review, and the conditional dependency estimated in RADicA and therefore were used to estimate the overall accuracy of diagnostic strategies in children. The same methodology was also used in the scenario analysis using a different value of sensitivity and specificity of FeNO in adults (see section 2.5.2).

This is one of the first applications of a multivariate probit for this purpose and its advantages and potential limitations are provided in the limitations section (see 4.2).

2.3.20 Optimal diagnostic strategies in adults and children

Table 8 summarises the diagnostic performance of each test in adults and children.

Table 8: Diagnostic accuracy of tests in adults and children

Tests	Adults		Children	
	Sensitivity	Specificity	Sensitivity	Specificity
Skin prick test	0.74	0.52	0.83	0.72
IgE	NA	NA	0.97	0.77
BDR	0.41	1.00	0.14	0.93
PEFv	0.15	0.97	0.45	0.92
Blood eosinophils	0.32	0.98	0.37	0.91
FeNO	0.53	0.87	0.32	0.99
Spirometry	0.37	0.96	0.68	0.76
Mannitol	0.63	0.93	0.64	0.95
Methacholine	0.62	1	0.9	0.82
Source	RADicA		Clinical review	

Abbreviations: BDR = bronchodilator reversibility; FeNO = Fractional exhaled nitric oxide; PEFv = Peak expiratory flow variability; STP = skin prick test

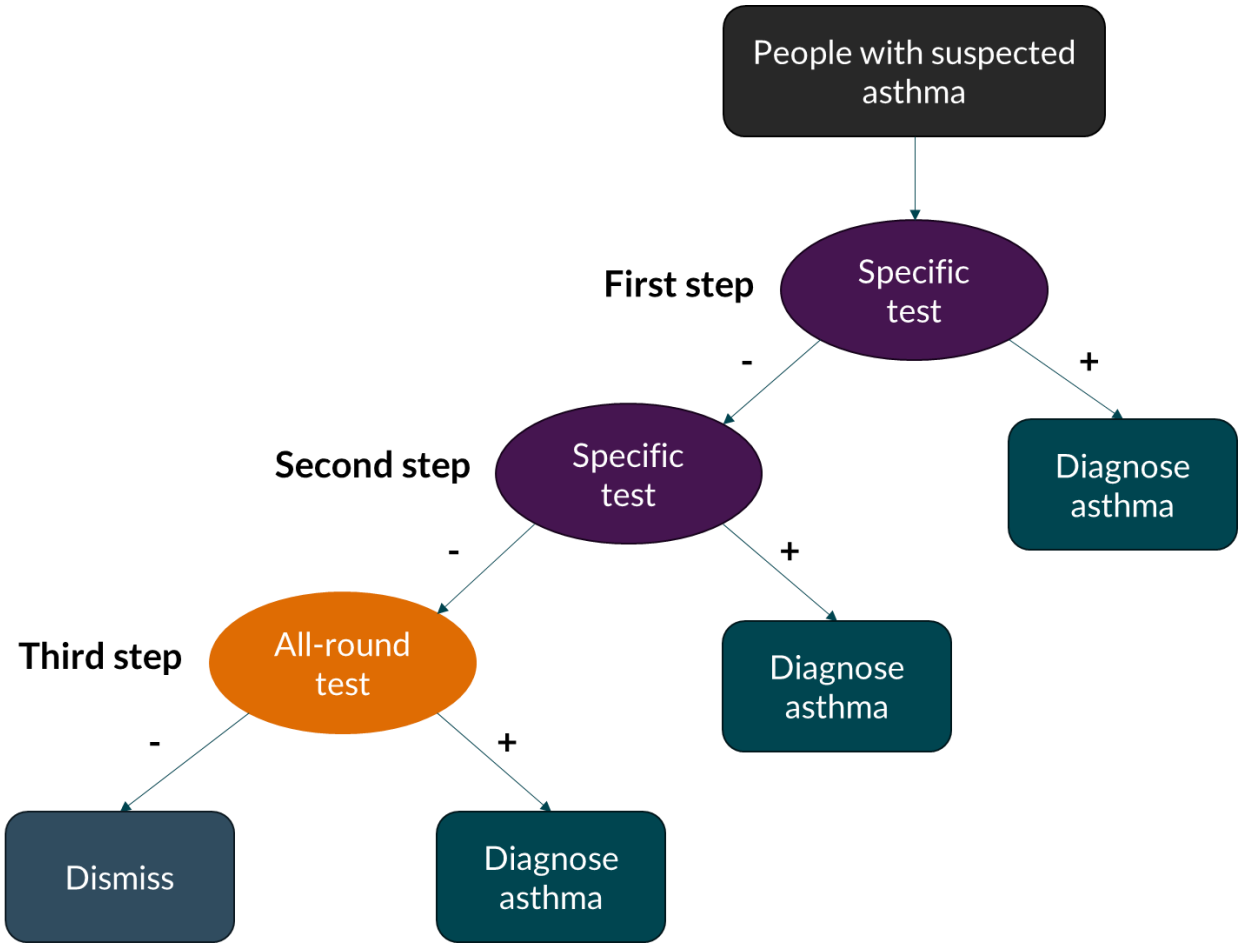
As the table shows, there is a range of tests that show high specificity but insufficient sensitivity in both adults and children: BDR, PEFv, blood eosinophils, FeNO. Bronchial challenge tests, either with mannitol and methacholine, showed high specificity and good or satisfactory sensitivity so they are considered "all-round" tests. Finally, whereas no test

demonstrated a good sensitivity in adults (> 0.8), both skin prick test and IgE exhibited good sensitivity and satisfactory specificity in children. Therefore, two different approaches were used when defined potential cost-effective strategies in adults and children.

For a particular sequence of tests to be cost-effective, each step should be designed to maximize the number of people that could be dismissed with a diagnosis before progressing to the subsequent step. Moreover, the least expensive tests should be given at the beginning of the sequence, targeting a wide population of people with suspected asthma, whereas the more expensive yet highly accurate tests should be reserved for the later stages, where fewer people with an uncertain diagnosis remain. Finally, tests that are either highly specific but poorly sensitive or vice versa should be given at the beginning of the sequence, as either those with a positive result or those with a negative result would need re-testing.

In adults, no highly sensitive test was available, so the model found that a “gradual rule-in” approach was the most cost-effective (see Figure 9).

Figure 9: Gradual rule-in approach: cost-effective strategies in adults

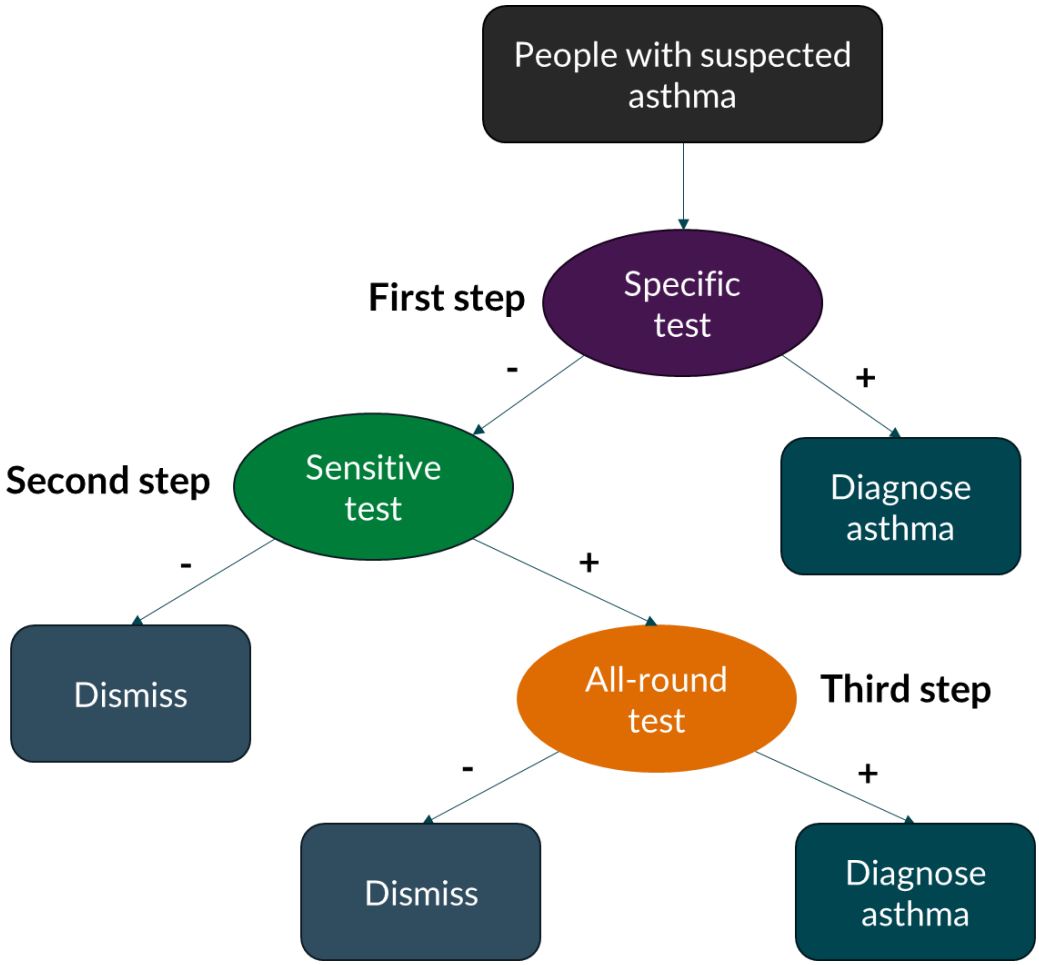


The approach consists in testing people with suspected asthma with an initial unexpensive but highly specific test. Those who test positive are immediately diagnosed with asthma (rule-in), as the high specificity of the test anticipates few false positives. Those who tested negative proceed to the second step where a second, uncorrelated specific test is given to further rule-in people before the final stage. Finally, the more expensive but “all-round” tests are reserved for those who remain undiagnosed even after the last ruling-in step.

The model found that all the most cost-effective strategies in adults reflect the structure defined above and the committee identified ten strategies that were included in the economic report (see Table 1).

In children, alongside several tests with good specificity, there were a few exhibiting good sensitivity: skin prick test and IgE. Therefore, the model found that a different approach, called “rule-in-rule-out”, was the most cost-effective (see Figure 10).

Figure 10: Rule-in-rule-out approach: cost-effective strategies in children



This approach involves testing all with an unexpensive but highly specific test in the first step, similarly to the approach in adults. Children who test positive can receive a diagnosis, whereas those who test negative will receive a further highly sensitive test. Using a sensitive test after a specific test, or vice versa, proved to be optimal as it allowed to either rule-out and rule-in a large proportion of children before the last step, which requires an all-round test (BCT).

The model found that all cost-effective strategies in children reflect the approach outlined above and ten were chosen by the committee to be included in this report (see Table 2).

When calculating the diagnostic accuracy of a test or a combination of tests, assuming independence between sensitivity and specificity in the probabilistic can lead to the incorrect estimation of uncertainty(Novielli, Cooper, Sutton, 2013). Therefore, the distribution around diagnostic odds ratio (DOR) was used to account for the inverse relationship between sensitivity and specificity following the methodology described by Genders and colleagues(Genders, et al., 2009).

First, diagnostic odds ratios were calculated using the following equation:

$$DOR = \frac{sens}{1 - sens} \times \frac{spec}{1 - spec}$$

Assuming a normal distribution of the logarithmically transformed DOR, standard error (SE) was calculated using equation 2:

$$SE(\ln(DOR) = \sqrt{\frac{1}{TP} + \frac{1}{FN} + \frac{1}{TN} + \frac{1}{FP}}$$

Finally, the resulting log-normal distribution of DOR was used to calculate probabilistic specificity values assuming a beta distribution for sensitivity:

$$Spec = \frac{DOR}{\left(DOR + \frac{sens}{1 - sens}\right)}$$

This methodology ensures that probabilistic values of sensitivity and specificity are not drawn independently but are inversely correlated at each simulation that is, when one is higher, the other is lower. This is expected to produce a more realistic estimation of uncertainty around diagnostic outcomes.

2.3.3 Natural history – asthma

The natural history of people with asthma (TP and FN) was simulated through the asthma management model described in section 2.2.1.2.

People first enter the short-term Markov model in either the TP or FN state in a proportion determined by the accuracy of the corresponding diagnostic strategy. They then transit to the long-term Markov model once all FN diagnoses are solved.

In each cycle, people can experience an asthma exacerbation or, if their asthma was diagnosed during childhood (before the age of 15), can achieve asthma remission.

2.3.3.1 Asthma exacerbations

An asthma exacerbation carries a different implication depending on whether it occurs in people with or without a diagnosis of asthma. In the former, it results in a temporary detriment to quality of life and increased healthcare cost. In the latter, in addition to quality of life and healthcare cost implications, an exacerbation leads to a new diagnosis of asthma, as the committee recognised that an asthma attack occurring in people who were initially dismissed would prompt further diagnostic assessment in secondary care, thereby revealing the presence of asthma. For this reason, asthma exacerbations were modelled with a different approach in people with and without a diagnosis of asthma.

2.3.3.1.1 Exacerbations in adults with a diagnosis

When occurring in people under treatment, exacerbations were estimated as annualised rates per patient year. These rates were subsequently multiplied by the number of patient years in each cycle to estimate the overall number of events occurring during a cycle.

Annualised rates were derived from the Novel START trial, a 52-week, randomised, international trial on three initial treatment options for asthma, which demonstrated the highest level of external validity(Beasley, Holliday, Reddel, Braithwaite, Ebmeier, Hancox, Harrison, Houghton, Oldfield, Papi, Pavord, Williams, Weatherall, Novel, 2019). In particular, the committee acknowledged that unlike other double-blinded trials(Bateman, Reddel, O'Byrne, Barnes, Zhong, Keen, Jorup, Lamarca, Siwek-Posluszna, FitzGerald, 2018) where

patients adherence was rigidly controlled, Novel START's pragmatic open-label design is more likely to reflect real-world behaviours and outcomes of asthma management.

Table 9 shows the rates used in the model, with inhaled corticosteroid and long-acting beta agonist (ICS/LABA) assumed to be the initial treatment in the base case scenario and inhaled corticosteroid plus short-acting beta agonist (SABA) tested in the sensitivity analysis.

Table 9: Annualised exacerbation rates

Treatment	Mean	LCI (95%)	UCI (95%)
ICS/LABA	0.195	0.14	0.274
ICS + SABA	0.175	0.131	0.254

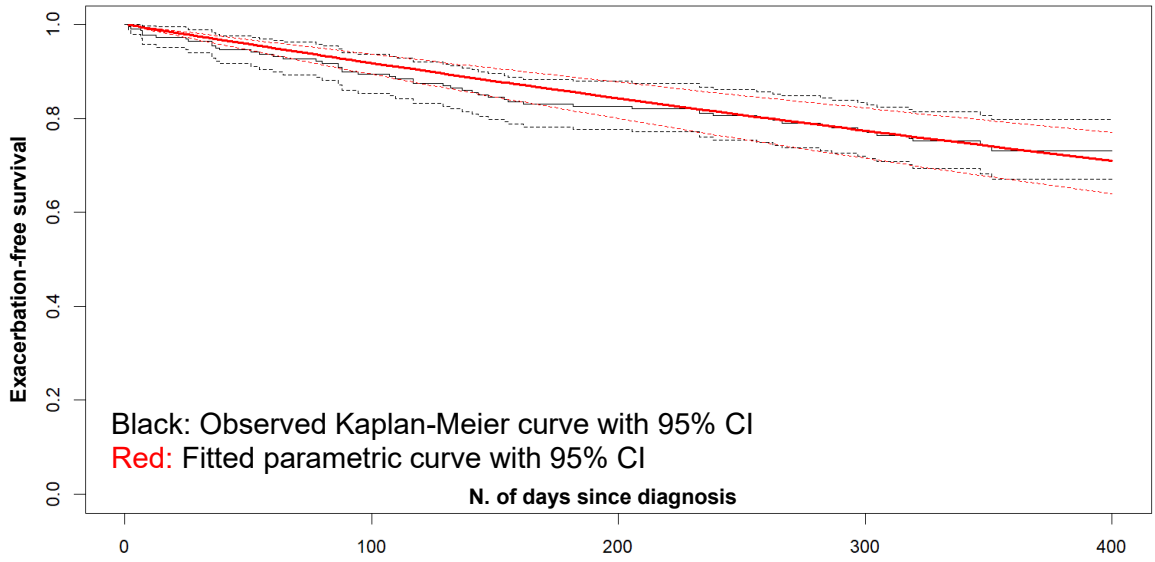
Exacerbations are not treated as a separate Markov state but are modelled as events occurring each cycle depending on the number of people at risk. The model then calculates the overall costs and quality-of-life detriment associated with the number of exacerbations the cohort experience during their lifetime, after accounting for discounting and half-cycle correction.

2.3.3.122 Exacerbations in adults without a diagnosis

As an asthma exacerbation occurring in people without a diagnosis of asthma prompts a new diagnosis, a time-to-event analysis (survival analysis) approach was adopted instead. Given the unavailability of natural history information on people with asthma who are untreated, we turned to data from the Novel START trial(Beasley, Holliday, Reddel, Braithwaite, Ebmeier, Hancox, Harrison, Houghton, Oldfield, Papi, Pavord, Williams, Weatherall, Novel, 2019), specifically focusing on people treated with SABA only. It is important to note that, while this population is undeniably under asthma treatment, SABA, unlike inhaled corticosteroid (ICS), primarily addresses acute asthma symptoms for rapid relief and serve as a rescue medication. As such, SABA's efficacy in preventing future exacerbation is questionable compared to ICS, which actively reduces airway inflammation over time. Therefore, the population using SABA alone more closely approximates the risk profile of people receiving no treatment at all. The implications of this assumption are further discussed in the limitations section (see 4.2).

The Kaplan-Meier curve describing time-to-first exacerbation in people receiving SABA alone was numerically extracted using WebPlotDigitizer(Automeris) and approximate patient-level data was reconstructed used the methodology outlined in Guyot 2012(Guyot, et al., 2012) and Wei 2017(Wei, et al., 2017). Pseudo IPD data were subsequently analysed in R studio, using the "survival" package, with the purpose of estimating a parametric survival curve that could be used to extrapolate the risk of exacerbation beyond the last follow-up time of the trial (52 weeks). A range of different distributions were explored with the log-logistic and exponential distribution emerging as the most fitting to the data. The log-logistic distribution showed the lowest Akaike Information Criterion (AIC) while the exponential distribution exhibited the lowest Bayesian Information Criterion (BIC). Ultimately, the exponential curve was preferred due to its relative simplicity and its more realistic predictions over the long-term, although the log-logistic was used in the scenario analysis. The reconstructed Kaplan-Meier and the fitted exponential parametric curves are shown in Figure 11.

Figure 11: Reconstructed Kaplan-Meier and fitted exponential curve – exacerbation-free survival



Cycle-specific transition probabilities of experiencing a first exacerbation were estimated using the parametric survival curve described above. Once an individual without a diagnosis experiences an asthma exacerbation, they move to the "treated" state upon undergoing further diagnostic examinations that revealed asthma. In this new state, the time-to-event analysis is not necessary, and new exacerbations are estimated using annualised event rates (see 2.3.3.1.1).

The committee acknowledged that people who are untreated might receive an asthma diagnosis even in the absence of an exacerbation episode, particularly if they return to primary care with persistent respiratory symptoms. The committee agreed that it was generally unlikely for asthma to go undiagnosed for more than two years, so the model assumes a maximum duration of two years spent without a diagnosis in the base case. Alternative maximum durations of one and five years were explored in the scenario analysis (see section 2.5.4).

2.3.3.1.3 Exacerbations in children

The committee were aware that the risk of exacerbation varies by age, as the rate is expected to be the higher in the elderly and the very young. To adjust the rates of exacerbation in a children population, a UK analysis(Chloe, Francis, Ian, Liam, Paul, Jennifer, 2018) based on primary and secondary care healthcare records (Clinical Practice Research Datalink, Hospital Episode Statistics, CPRD-HES) was utilised. The study estimated the rate of exacerbation per 10 person-years in different age group. For this analysis, we selected three age groups: under 5s, representing the infant population, 5 to 17s representing children and 18 to 54s, representing the adult population. Using the adult group as a reference, incident rate ratios were calculated for the infant and children groups (see Table 10).

Table 10: Exacerbations by age groups

Population	Rate of exacerbations per 10 person-years	Total cohort	Incident rate ratios (IRR) [a]
Under 5s – infants	4.27 (4.18 to 4.38)	17,320	1.33
5 to 17s – children	1.48 (1.47 to 1.50)	82,707	0.46

Population	Rate of exacerbations per 10 person-years	Total cohort	Incident rate ratios (IRR) [a]
18 to 54s – adults	3.22 (3.21 to 3.24)	210,724	1 (reference)

(a) Incident rate ratios (IRR) calculated as rate in infants/children divided by rate in adults
Source: Bloom 2018(Chloe, Francis, Ian, Liam, Paul, Jennifer, 2018)

The incident rate ratios calculated in Table 10 were multiplied for the annualised exacerbation rates in adults to estimate the number of exacerbations in an infant and children population.

Time-to-first exacerbation in those who are untreated was also adjusted in the children cohorts using the same source. Median times to first exacerbation were extracted from the study using WebPlotDigitizer(Automeris) and are reported in Table 11.

Table 11: Median time to first exacerbation

Population	Rate of exacerbations per 10 person-years	Hazard ratios (HR) [a]
Under 5s – infants	2.83 years	1.24
5 to 17s – children	8.5 years	0.41
18 to 54s – adults	3.5 years	1 (reference)

(a) Incident rate ratios (IRR) calculated as rate in infants/children divided by rate in adults
Source: Bloom 2018(Chloe, Francis, Ian, Liam, Paul, Jennifer, 2018)

The figures in Table 11 were used to calculate hazard rates and hazard ratios (Table 11) using the following formulae(NCSS Statistical Software, 2024):

$$h = \frac{\ln(2)}{MET}$$

$$HR_{5-17} = \frac{h_{5-17}}{h_{18-54}}$$

where h is the hazard rate, MET is the median exacerbation time, and HR_{5-17} is the hazard ratio of first exacerbation between children aged 5 to 17 and the adult cohort. These hazard ratios were used to adjust the time-to-first exacerbation in an untreated infant (0 – 4) and children cohorts (5 –17) by applying them to the hazard rates derived from the parametric curve estimated in the time-to-event analysis described in section 2.3.3.1.2.

2.3.3.1.2 Remission

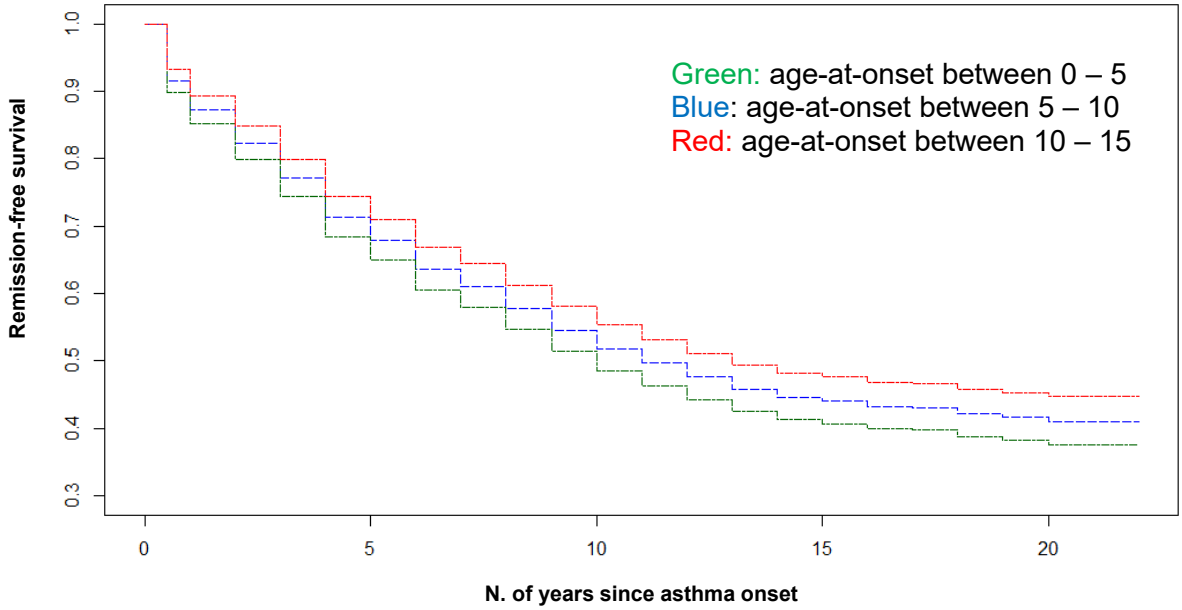
The academic literature(De Marco, Locatelli, Cerveri, Bugiani, Marinoni, Giammanco, 2002, Fuchs, et al., 2017) commonly describes two different forms of asthma with distinct features in natural history and prognosis: early-onset asthma and late-onset asthma. The latter generally manifests after puberty and is associated with a more chronic and persistent form of the disease and a very low likelihood of remission. Conversely, early-onset asthma, which occurs early during childhood, is associated with a favourable prognosis and a high likelihood of complete remission before reaching adulthood.

For this reason, the committee agreed to incorporate remission only in the children analysis. A relevant retrospective study(De Marco, Locatelli, Cerveri, Bugiani, Marinoni, Giammanco, 2002) on the natural history of asthma was identified in the literature. The study found that remission was strongly influenced by the age at onset, with very young children achieving high rates of remissions (around 60%). The study presented multiple Kaplan-Meier curves showing the cumulative probability of remission within distinct cohorts characterized by the

age of asthma onset. For this analysis, we focused on three age-at-onset groups, 0 – 5, 5 – 10 and 10 – 15. Numerical data was extracted from the three Kaplan-Meier curves using WebPlotDigitizer(Automeris) and pseudo IPD was reconstructed using the methodology illustrated in Guyot 2012(Guyot, Ades, Ouwens, Welton, 2012) and Wei 2017(Wei, Royston, 2017). As numbers at risk were not reported in the original study, we assumed constant censoring over time. This represents a clear simplification as censoring is often not constant and could be influenced by the outcome of interest. For instance, people may withdraw from the study upon achieving remission without recording the event. In such scenarios, uncertainty in the right tail of the curve might be underestimated, potentially resulting in a sub-optimal specification of the parametric survival curve. However, this was a pragmatic decision as the alternative option of assuming no censoring would certainly introduce more biases.

Reconstructed Kaplan-Meier curves for 0 – 5, 5 – 10 and 10 – 15 age-at-onset groups are illustrated in Figure 12.

Figure 12: Reconstructed Kaplan-Meier cumulative curves of remission-free survival



The data was analysed using the “survival” package of R studio and several parametric curves were fitted to the data. The lognormal mathematical distribution was identified as the best fit (lowest AIC and BIC) and used to extrapolate parametric curves over a lifetime for the three age-at-onset groups (Figure 13, Figure 14, Figure 15)

Figure 13: Observed and parametric remission-free survival – age 0 to 5

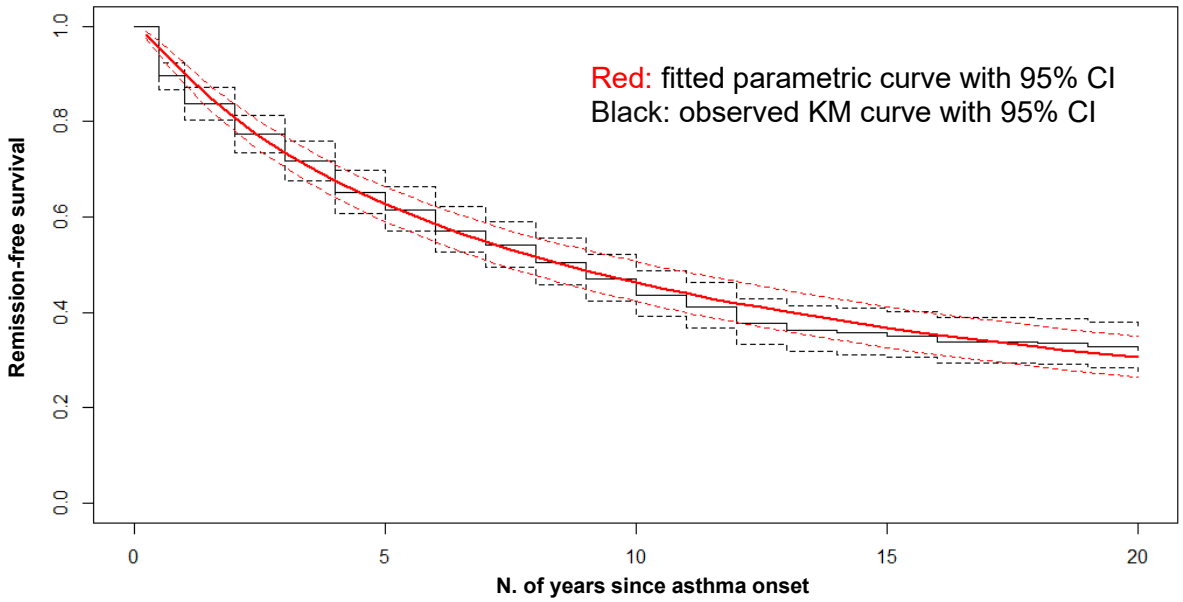


Figure 14: Observed and parametric remission-free survival – age 5 to 10

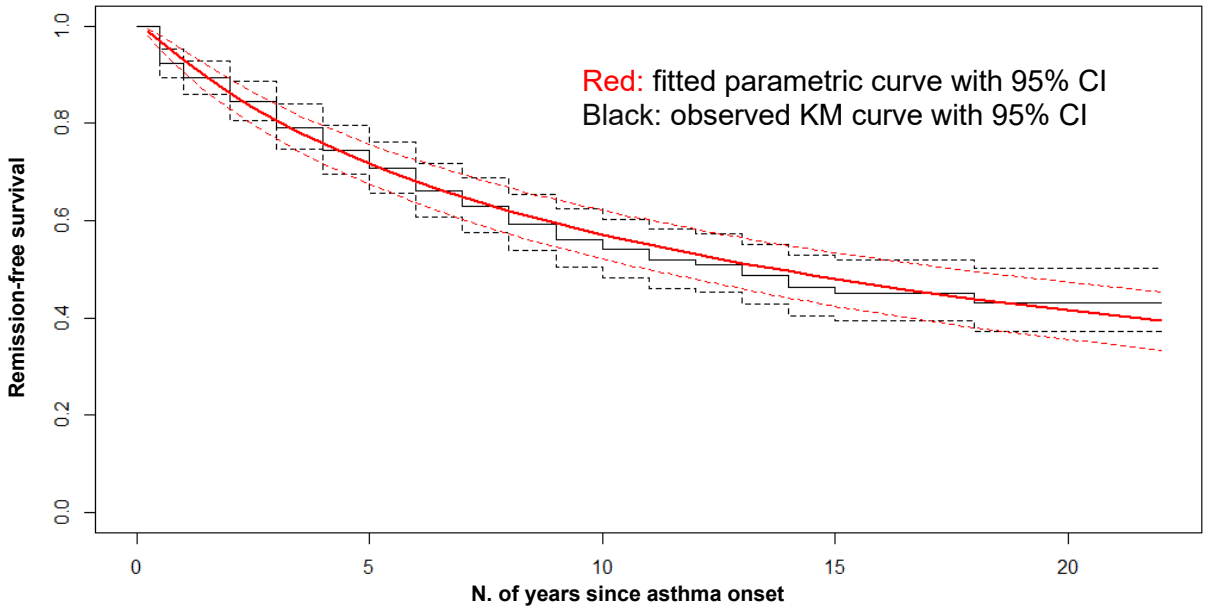
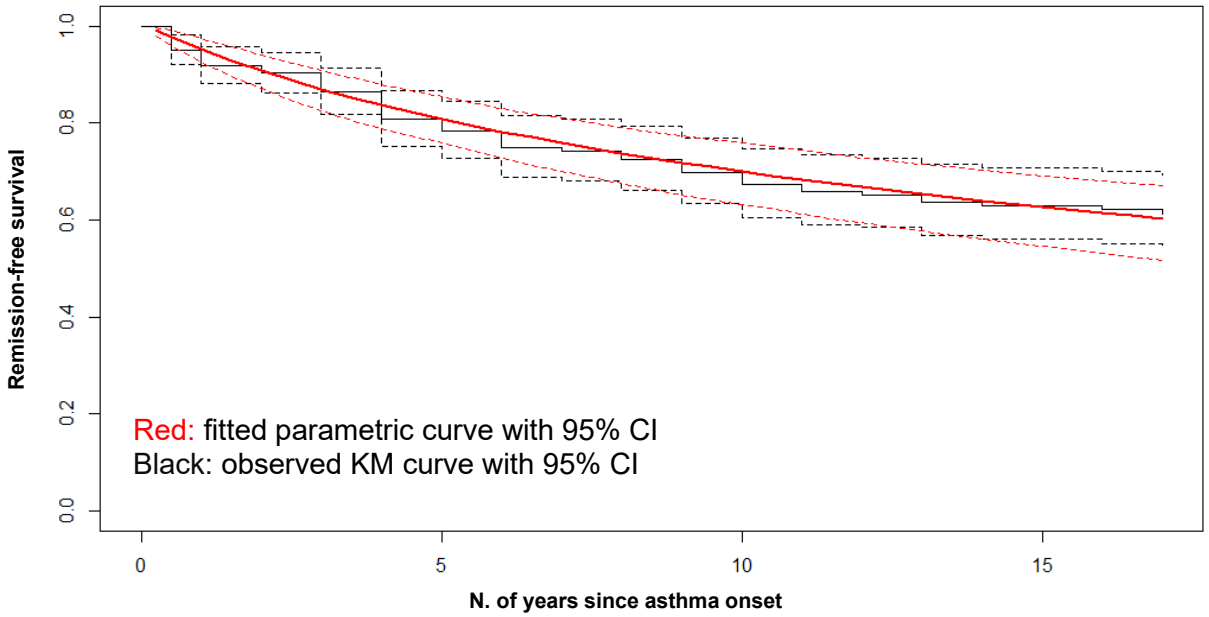


Figure 15: Observed and parametric remission-free survival – age 10 to 15



The lognormal parametric curves defined above provided predictions that closely matched real-world expectations, as the committee were aware that around 50% of people whose asthma was diagnosed during childhood would achieve remission within 20 years. As they agreed that it was unlikely that remission could be achieved after 20 years, an assumption was made to preclude remission beyond 20 years from the onset of asthma.

Monthly and yearly transition probabilities were calculated based on the lognormal parametric curves and applied in the short-term and long-term Markov model, respectively. Upon achieving remission, people were assumed to discontinue their asthma treatment and return to the general population mortality, although a different quality of life multiplier was applied (see 2.3.6.1). While there are instances where people who have experienced remission may later exhibit remitting-relapsing symptoms of asthma(Fuchs, Bahmer, Rabe, von Mutius, 2017), no quantitative evidence on this phenomenon was identified. Consequently, the model assumes that remission, once achieved, is everlasting (see section 4.2).

2.3.4 Natural history – without asthma

The natural history of people without asthma (TN and FP) was simulated through the non-asthma management model described in section 2.2.1.3.

People who were found to be without asthma are assumed to be referred for subsequent diagnostic examinations and, if necessary, treatment for their underlying condition. As a result, no additional costs, quality of life deterioration, or mortality effect is applied. This is appropriate as any treatment cost or quality-of-life effect associated with a condition other than asthma are out-of-scope for this analysis.

People who were erroneously diagnosed with asthma are treated and monitored for this condition. However, it is assumed that their symptoms would not improve, as the committee were aware that asthma treatments may not necessarily alleviate symptoms associated with other respiratory conditions. Moreover, it assumed that people treated for asthma would not receive the appropriate treatment for their underlying condition until their diagnosis is corrected. Therefore, the model applies a diminishing quality-of-life multiplier in this state,

assumed to be equivalent to those with asthma, given the presence of asthma-like symptoms in this population.

People undergoing treatment for asthma, despite not having the disease, can have their diagnosis corrected over time, transitioning to the true negative state. The proportion of people on treatment at each year was estimated by applying a parametric survival equation that was fitted on data a Canadian longitudinal(Aaron, et al., 2008, Pakhale, Sumner, Coyle, Vandemheen, Aaron, 2011) study. In this study, Canadian patients who reported a physician diagnosis of asthma were randomly selected and underwent a series of lung function tests to determine if their diagnosis was correct. Further details of the study design, subject recruitment, and methods are described elsewhere(Aaron, Vandemheen, Boulet, McIvor, FitzGerald, Hernandez, Lemiere, Sharma, Field, Alvarez, Dales, Doucette, Fergusson, 2008).

The underlying numerical data of the study were extracted from a figure published in an economic evaluation(Pakhale, Sumner, Coyle, Vandemheen, Aaron, 2011) using WebPlotDigitizer(Automeris). As information on number of people at risk was not available, a pseudo IPD could not be reconstructed so, instead, a parametric curve was directly fitted to the extracted numerical data using “fitdistrplus” package in R studio. A Weibull curve with a shape of 1.11 and a scale of 0.37 was identified as the best fit as it had the lowest Cramer-von Mises and Anderson-Darling statistics and the second lowest Kolmogorov-Smirnov statistic (compared to a gamma and a lognormal distribution). Akaike's and Bayesian information criteria were comparable between the Weibull and lognormal distributions so the first was preferred due to the better goodness-of-fit- statistics. The distribution parameters were made probabilistic assuming that their logarithmically transformed values would be normally distributed. Observed and extrapolated curves representing the proportion of people being on treatment despite not having asthma at each year is presented in Figure 16.

Figure 16: Cumulative probability of being on treatment despite not having asthma

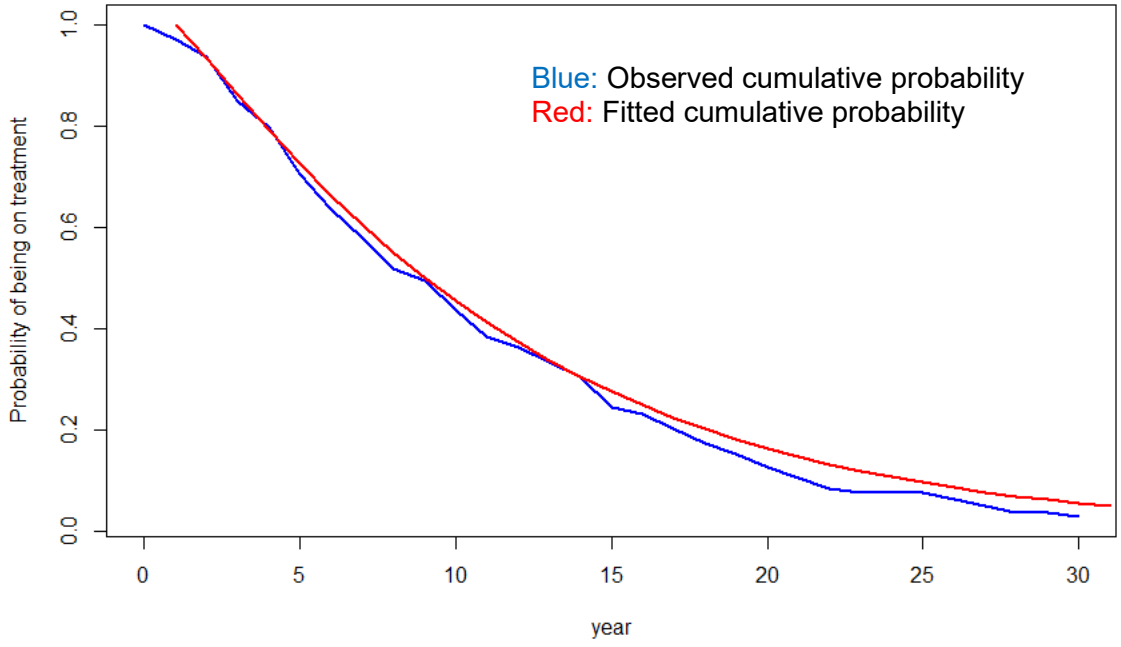


Figure 16 shows that although more than 50% of people are expected to discontinue asthma treatment within a decade of diagnosis, a significant proportion of people remain on treatment for an extended prior of time. This aligned well with the committee’s experience, as they were aware that many of those currently undergoing asthma treatment may not truly have the condition.

The estimated parametric curve and a survival curve based on either English or Scottish national life tables(Office for National Statistics, 2021) were combined to determine the proportion of people in each of the three mutually exclusive state at any year. This allowed to calculate lifetime costs and quality of life implications of misdiagnosis asthma on those without the disease.

2.3.5 Mortality

2.3.5.1 General population mortality

General population mortality was estimated using Office of National Statistics (ONS) National Life Tables (2018 – 2020)(Office for National Statistics, 2021). England- and Scotland-specific lifetables were used for the two different settings (see 2.5.7). A pragmatic choice was made to avoid using more recent publications to exclude excess mortality associated with the 2020 Coronavirus pandemic.

Survival curves were generated based on Life Tables' mortality rate, cycle-specific gender split and age of the cohort. These were used to calculate the risk of dying for people who do not have asthma or for those achieving remission. In the short-term Markov model, annual rates were first transformed into monthly rates to reflect the cycle length.

2.3.5.2 Mortality in people with asthma

People with asthma are at a higher risk of mortality compared to the general population. This is not only because a severe asthma exacerbation can, in rare circumstances, lead to death but largely due to the association between asthma and various other health risks including conditions such as depression, COPD, coronary, heart disease, cerebrovascular disease, and heart failure(Iribarren, et al., 2012). If survival in people with asthma is not adequately captured, there is a risk that the model could overestimate or underestimate the life-expectancy and, consequently, healthcare utilisation among people with asthma.

This analysis used two studies to estimate survival with asthma. The first is a Finnish population-based matched cohort study with a 15-year follow-up on 1,640 asthma patients older than 30 years old(Lemmetyinen, Karjalainen, But, Renkonen, Pekkanen, Toppila-Salmi, Haukka, 2018). People from the study were matched with one or two controls without asthma controlling for age, gender and area of residence. The study found a statistically significant increased all-cause mortality associated with asthma (adjusted HR 1.25; 95% CI 1.05 – 1.49, p = 0.01). This hazard ratio was applied in the model to estimate mortality among adults with asthma (older than 18).

To estimate mortality in children, a second study was identified that linked Scotland-wide individual-level data from different health databases and included 45,900 children with asthma(Fleming, Fitton, Steiner, McLay, Clark, King, Mackay, Pell, 2019). After adjusting for sociodemographic and maternity factors, the study found asthma to be a statistically significant factor increasing all-cause mortality (HR 1.77; 95% CI 1.30 – 2.40). This hazard ratio was used in the model to estimate mortality among children with asthma (younger than 18).

Table 12: Mortality hazard ratios

Population	Hazard ratio (95% CI)	Source
Adults (>18)	1.25 (1.05 to 1.49)	Lemmetyinen 2018(Lemmetyinen, Karjalainen, But, Renkonen, Pekkanen, Toppila-Salmi, Haukka, 2018)

Population	Hazard ratio (95% CI)	Source
Children (<18)	1.77 (1.30 to 2.40)	Fleming 2019(Fleming, Fitton, Steiner, McLay, Clark, King, Mackay, Pell, 2019)

2.3.5.3 Excess mortality with untreated asthma

People whose asthma is untreated due to a misdiagnosis are at a higher risk of mortality due to an increased risk of asthma attacks and hospitalisations. As mentioned in 2.3.3.1.2, there is no natural history study looking at mortality in untreated people with asthma, so excess mortality was extrapolated from a proxy population. Suissa and colleagues(Suissa, Ernst, Benayoun, Baltzan, Cai, 2000) followed 30,569 individuals for a period of 15 years and matched cases of people who died of asthma with control cases. They found that the rate of asthma-related mortality in individuals using a minimum of six canisters of inhaled corticosteroids (ICS) annually was only 50% of the rate observed among non-users. Using these findings, excess mortality in people with untreated asthma was calculated using the following formulae:

$$CFR = \frac{N.of\ asthma\ deaths}{N.of\ people\ with\ asthma}$$

$$CFR_{untreated} = \frac{CFR}{RR}$$

$$Excess\ mortality = CFR_{untreated} - CFR$$

In the first equation, caser fatality rate (CFR), defined as the proportion of people with asthma dying each year because of the disease, was calculated by dividing the number of asthma-related deaths in 2022 (ONS 2022(Office for National Statistics, 2023)) by the number of people who are currently receiving treatment for asthma in the UK(National Institute for Health and Care Excellence, 2023).

In the second equation, case fatality in people with untreated asthma was estimated by dividing case fatality by the risk ratio reported in Suissa 2000 (0.5).

Finally, in the third equation, excess mortality was estimated by taking the difference between the case fatality rate in people who are untreated and the case fatality rate in those who are treated. Hence, excess mortality offers an estimation of the additional mortality expected in people who are untreated and was applied in the short-term Markov model to those who have a false negative diagnosis. Other asthma-related case fatality rates were not used to avoid double counting, as asthma-related deaths in people who are treated are expected to be already factored into the increased asthma mortality reported in the literature.

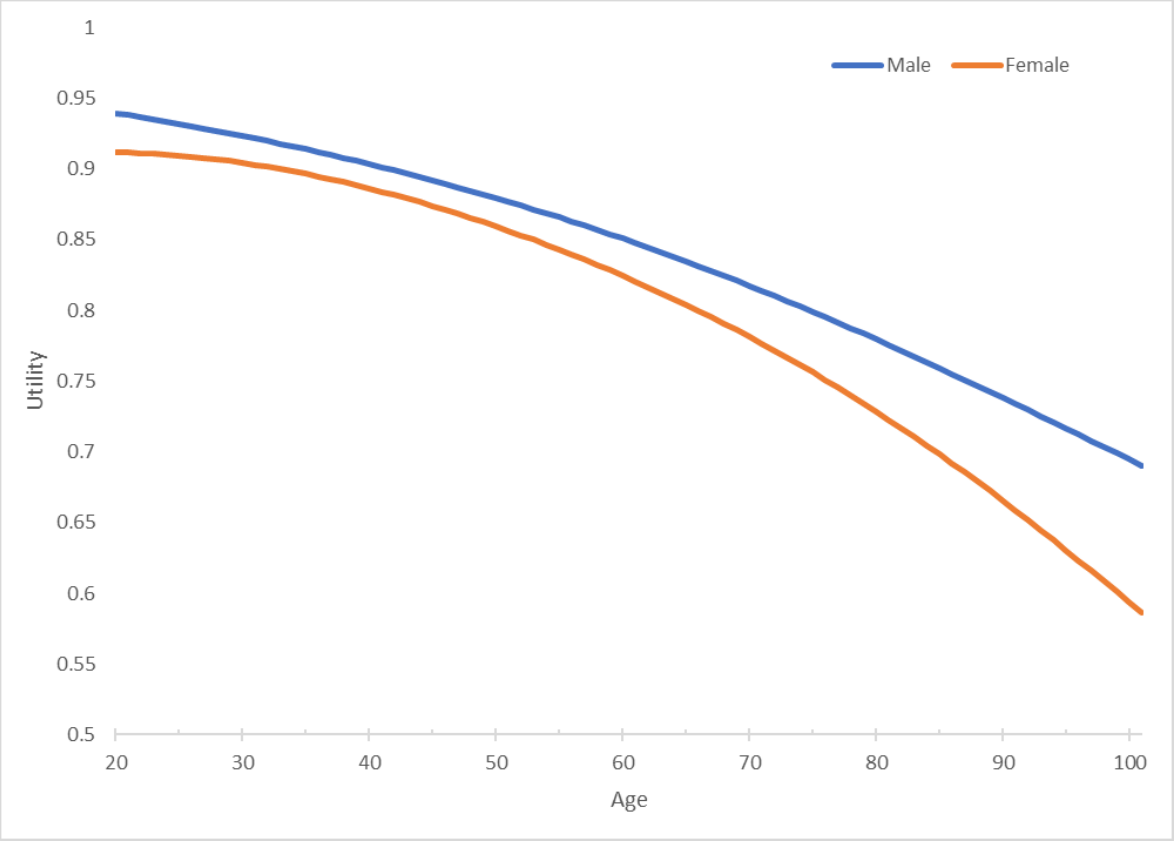
2.3.6 Utilities

2.3.6.1 Quality of life with asthma

Age- and sex-specific quality of life scores ('utilities') were used in the model. Utilities in the general population were derived using an Adjusted Limited Dependent Variable Mixture Model (ALDVMM) based on Health Survey for England data as reported in a publication by the NICE Decision Support Unit(Alava, Pudney, Wailoo, 2022) (see Figure 17). In people

younger than 20, we assumed an utility score of 1 (equal to “perfect health”) as no relevant study in this group was identified.

Figure 17: General population utility scores



The impact on quality of life associated with asthma was estimated through a bespoke analysis of the Health Survey for England (HSE). The HSE is a survey conducted on a random sample of residents in England and covers a range of aspects including socio-economic factors, demographics, and health indicators. The 2018 survey(NHS Digital, 2019) focused on respiratory conditions and included valuable information such as a history of asthma attacks, diagnosis, and asthma control. Participants were asked whether they have a doctor-diagnosed asthma and whether they had any symptoms of asthma in the last 12 months. For this analysis we focused on three categories of people:

- People on asthma medication with or without symptoms in the last 12 months reflecting the average population receiving treatment for asthma in England
- People who have had symptoms of asthma in the last 12 months despite being on asthma medication, representing the population whose asthma is inadequately controlled by current treatment
- People with no symptoms of asthma and who are not on asthma medication reflecting those who have achieved remission

To estimate the average quality of life in the three groups, we looked at the responses to the EQ-5D-5L questionnaire. NICE does not currently endorse the use of EQ-5D-5L for directly calculating utility values but, instead, recommends using EQ-5D-3L value in the reference case(National Institute for Health and Care Excellence, 2019). Therefore, 5L values were firstly mapped into 3L values using the “crosswalk” function developed by Van Hout and colleagues(van Hout, et al., 2012).

People with asthma were matched to other participants of the survey after controlling for age and gender. Subsequentially, utility multipliers were calculated using the following equation:

$$Multiplier = Avg\left\{\frac{U_{asthma}}{U_{general}}\right\}$$

where U_{asthma} is the average utility of people with asthma within a specific matching group, defined by gender and age, and $U_{general}$ is the average utility of all participants within the same group. The overall utility multiplier was estimated by taking a weighted average across all the matching groups. The analysis was done using Stata v13(StataCorp, 2023).

Three multipliers were estimated for the three groups outlined above (see Table 13).

Table 13: Utility multipliers

Population	Utility multiplier [(a)]	Source
People on asthma medication	0.880 (0.064)	Health Survey for England 2018
People on medication and uncontrolled asthma	0.819 (0.011)	
People without medication with controlled asthma	0.989 (0.052)	

(a) Average utility of people with asthma divided by the average utility of the general population adjusted for gender and age group. Average value with standard deviations in parentheses

A multiplier provides an estimate of how the quality of life of people with a particular condition is reduced compared to the general population. Table 13 shows that people with asthma have, on average, 12% less utility than general population and, if the asthma is uncontrolled, 18% less. People with controlled asthma and are not in medication have a quality of life close to the general population.

These values were multiplied by age- and gender- specific general population utility values to estimate utility associated with various health states. The first multiplier for people with asthma was applied to people undergoing asthma treatment, regardless of whether they have asthma or not (TP and FP). This is appropriate for two reasons: firstly, this value was estimated using a real-world survey of people on asthma medication in England, where a significant proportion are anticipated to lack the actual medical condition(Shaw, Green, Berry, Mellor, Hargadon, Shelley, McKenna, Thomas, Pavord, 2012). Therefore, it reflects the average utility of people with and without asthma being treated for this condition. Secondly, people who do not have asthma but are erroneously being treated for it, might have persistent asthma-like respiratory symptoms, which justifies the use of the same multiplier.

The second multiplier, related to people with uncontrolled asthma, was applied to people with asthma who are presently untreated (FN). This is because symptoms of asthma are expected to be inadequately controlled and potentially exacerbated in the absence of treatment. The committee acknowledged that many of those whose asthma remain undiagnosed following objective diagnostic tests may have a mild or intermittent form of the disease. In such cases, even if left untreated, these forms of asthma might exert a limited impact on people's quality of life. Therefore, a scenario analysis was included in which people with untreated asthma were assumed to share the same quality of life of those receiving treatment.

The third multiplier, calculated based on HSE participants reporting no asthma symptoms despite not receiving any treatment, was applied to people who ceased their medication after achieving remission.

2.3.6.12 Quality of life after an exacerbation

Exacerbations are serious complications of asthma that are characterised by a progressive worsening of bronchial obstruction, leading to shortness of breath, coughing, wheezing and/or chest tightness(Reddel, et al., 2009). An exacerbation is considered severe if the symptoms are particularly worrying and require systematic corticosteroids or a hospitalisation. To estimate the impact of a mild/moderate and severe exacerbation to quality of life, we used a post-hoc analysis of a multi-national trial investigating exacerbations among 485 patients(Briggs, Nasser, Hammerby, Buchs, Virchow, 2021).

The impact on participant's quality of life was measured using EQ-5D-3 by mapping Asthma Quality of Life Questionnaire into EQ-5D-3L dimensions. The average duration of an exacerbation was ascertained using patient electronic diaries reporting lung function. The authors found that lung function started to decrease 14 days before an exacerbation, followed by a gradual return to baseline over 14 days. Differences in utility between people experiencing exacerbations and those with a normal lung function were collected at 7, 14, 21 and 28 days from the beginning of the episode (see Table 14).

Table 14: Impact of moderate and severe exacerbations on utility

Days since event	Moderate exacerbation	Severe exacerbation
7 days	- 0.0921 (0.0059)	- 0.163 (0.0118)
14 days	- 0.0876 (0.0055)	- 0.132 (0.0096)
21 days	- 0.0867 (0.0054)	- 0.125 (0.0095)
28 days	- 0.0834 (0.0053)	- 0.115 (0.0090)

Note: Standard errors in parentheses

Overall utility detriments caused by a moderate or severe exacerbation were calculated by taking an average of the values reported at each follow-up in Table 14. The reduction in quality-adjusted-life-years (QALYs) associated with a moderate severe exacerbation was then estimated assuming that an event would last, on average, 28 days as shown in Briggs 2021(Briggs, Nasser, Hammerby, Buchs, Virchow, 2021) (see Table 15**Error! Reference source not found.**).

Table 15: Utility detriment and QALYs loss after an exacerbation in adults

Event	Utility detriment	Duration	QALYs loss [(a)]
Moderate exacerbation	0.087	28 days	0.007
Severe exacerbation	0.134	28 days	0.010

(a) Calculated as utility detriment multiplied by duration divided by 365
Source: Briggs 2021(Briggs, Nasser, Hammerby, Buchs, Virchow, 2021)

The model used the QALYs loss values reported in Table 15 to estimate the overall impact on quality of life attributable to moderate and severe exacerbations occurring in each cycle.

The proportions of exacerbations that are moderate or severe was derived from the Novel START trial(Beasley, Holliday, Reddel, Braithwaite, Ebmeier, Hancox, Harrison, Houghton, Oldfield, Papi, Pavord, Williams, Weatherall, Novel, 2019) and are reported in Table 16. For people under treatment, we used the proportion among those on ICS/LABA, which is the standard treatment in the base case scenario. For people who are untreated, the proportion observed in people on SABA alone was applied, as this was considered a proxy population for the untreated cohort.

Table 16: Exacerbations categorisation

Population	% of mild/moderate exacerbation	% of severe exacerbation
People treated for asthma [(a)]	76%	24%
People untreated [(b)]	69%	31%

(a) Using the proportion of the ICS/LABA arm
(b) Using the proportion of the SABA alone arm

2.3.63 Quality of life in children with asthma

While the Health Survey for England (HSE) included participants younger than 16, EQ-5D-5L questionnaire is exclusively validated for use in adult populations and was not recorded in children. Consequently, a systematic review of health states utilities in children with asthma was used instead(Kua, Davis, 2016). The review identified a quality-of-life study in children in Netherlands(Willems, et al., 2007), using the children version of the EQ-5D questionnaire and UK preferences, that was used in another UK economic evaluation(Horspool, et al., 2013). Although the results were elicited from a non-UK population, the study meets NICE reference case and therefore was used in this analysis.

Table 17: Quality of life in children

Population	Health utility values[(a)]	Measurement	Source
Children with no exacerbation	0.96 (0.07)	EQ-5D child version (filled out by parent for age<12). UK adult TTO valuation set	Willems 2007(Willems, Joore, Hendriks, Wouters, Severens, 2007)

(a) Mean value with standard deviation in parentheses

There was no study looking at the impact of asthma exacerbation specifically on children so the same values estimated for adults were used(Briggs, Nasser, Hammerby, Buchs, Virchow, 2021). Nevertheless, the committee recognised that an exacerbation is generally shorter in children, so the lower estimate of 20 days was used instead of the 28 assumed in adults (see Table 18).

Table 18: Utility detriment and QALYs loss after an exacerbation in children

Event	Utility detriment	Duration	QALYs loss [(a)]
Moderate exacerbation	0.087	20 days	0.005
Severe exacerbation	0.134	20 days	0.007

(a) Calculated as utility detriment multiplied by duration divided by 365
Source: Briggs 2021(Briggs, Nasser, Hammerby, Buchs, Virchow, 2021)

2.3.64 Resource use and costs

2.3.65 Healthcare professional costs

The cost per patient facing hour and per visit of practice nurses and general practitioners (GP) were collected from the 2022 publication of the Personal Social Services Research Unit (PSSRU)(Jones, Birch, Dargan, Forder, Roland). The costs are shown in Table 19 and include qualification costs but exclude individual and productivity costs. The cost of a specialist visit was estimated from the National Cost Collection for the NHS as a weighted average between all the codes within the “respiratory medicine” category.

Table 19: Costs of healthcare professionals

Health care professional (HCP)	Cost per hour per patient contact	Cost per visit	Source
GP	£244	£38	PSSRU 2022(Jones, Birch, Dargan, Forder, Roland)
Practice nurse	£63.38	£16.39	PSSRU 2022(Jones, Birch, Dargan, Forder, Roland)
Outpatient visit	NA	Adults: £185 Children: £266	National Cost Collection 2021/2022(NHS England, 2022)
Consultant led visit	NA	Adults: £194 Children: £301	National Cost Collection 2021/2022(NHS England, 2022)

Note: all costs include qualification costs excluding individual and productivity costs

Information on the time and health care professional required from each test were provided by the committee and used to calculate the cost of all tests included in the analysis (see section 2.3.7.2).

2.3.7.2 Diagnostic tests

Most tests were costed using a bottom-up approach, drawing on information provided by the committee, national healthcare sources and, when necessary, personal communication with the manufacturers. The costs of bronchial challenge tests with methacholine or mannitol and blood tests were sourced from the National Cost Collection for the NHS(NHS England, 2022).

Table 20 illustrates the consumables and staff time factored into the estimation of the cost of a spirometry. The cost of consumables that are expected to be used over a long period of time were annuitized using information provided in the technical manual of the device and a discounting factor of 3.5%.

Table 20: Cost of spirometry test

Resource	Quantity	Unit costs	Total cost	Source
MicroLab with integral printer and spirometry PC software	1/2100 [a]	£1,174.13 per spirometer	£0.62	NHS Supply Chain Catalogue(NHS Supply Chain Catalogue., 2022)
Calibration syringe 3 litre	1/2100 [a]	£231.69 per syringe	£0.12	NHS Supply Chain Catalogue(NHS Supply Chain Catalogue., 2022)
Bacterial filter plus mouthpiece	1	£1.06 per filter and mouthpiece	£1.06	NHS Supply Chain Catalogue(NHS Supply Chain Catalogue., 2022)

Resource	Quantity	Unit costs	Total cost	Source
Time of practice nurse	20 minutes	£63.38 per hour	£21.13	PSSRU 2022(Jones, Birch, Dargan, Forder, Roland)
Total cost	**£22.93**			

Note: all prices are VAT exclusive
(a) Assuming that the equipment would last for 7 years and used on average 2100 times(MicroDirect, 2019) during that period. Annuitisation was undertaken assuming a rate of 3.5%

Table 21 illustrates the methodology used to calculate the cost of a bronchodilator reversibility test. The cost of two spirometries were fed into the calculation, as people undergoing a BDR would receive a spirometry before and after taking salbutamol. The salbutamol inhaler was assumed to be reusable after the test, as it is provided through a spacer.Table 20

Table 21: Cost of bronchodilator reversibility test

Resource	Quantity	Unit cost	Total cost	Source
Spirometry	2	£1.8 per spirometry	£3.6	NHS Supply Chain Catalogue(NHS Supply Chain Catalogue., 2022)
Salbutamol reusable inhaler	400 mcg	£0.0001 per mg	£0.04	BNF(Joint Formulary Committee, 2024) and PCA(NHS Business Services Authority, 2021)
Spacer device for use with MDI without mask	1	£3.83 per spacer	£3.83	NHS Supply Chain Catalogue(NHS Supply Chain Catalogue., 2022)
Time of practice nurse	30 minutes	£63.38 per hour	£31.69	PSSRU 2022(Jones, Birch, Dargan, Forder, Roland)
Total cost	**£39.16**			

Note: all prices are VAT exclusive

Table 22 shows the approach used to cost a PEFv test. There was some uncertainty around the staff time required as, contrarily to the other tests, PEFv is performed by patients themselves, with healthcare professionals only need for the explanation and results interpretation. Therefore, two different values were explored, with the base case scenario assuming 20 minutes and a further scenario using 10 minutes.

Table 22: Cost of Peak Flow Measurement variability test (PEFv)

Resource	Quantity	Unit cost	Total cost	Source
Adult mini-wright peak flowmeter	1	£4.65 per flowmeter	£4.65	NHS Supply Chain Catalogue(NHS

Resource	Quantity	Unit cost	Total cost	Source
				Supply Chain Catalogue., 2022)
Low range mini-wright paediatric	1	£4.75 per flowmeter	£4.75	NHS Supply Chain Catalogue(NHS Supply Chain Catalogue., 2022)
Time of practice nurse	10 – 20 minutes[(a)]	£63.38 per hour	£10.57 - £21.13	PSSRU 2022(Jones, Birch, Dargan, Forder, Roland)
Total cost – adults	**£15.22 - £25.78**			
Total cost – children	**£15.32 - £25.88**			

Note: all prices are VAT exclusive
(a) 20 minutes assumed in the base case scenario

To estimate the cost of a FeNO test, information was obtained from the manufacturer of NIOX VERO, one of the most commonly used FeNO device in the UK. Expected lifetime, device and consumable prices were used to calculate the annuitized mean per-test cost across three scenarios, characterized by a different annual volume (Table 23).

Table 23: Annuitized cost of a FeNO device

Characteristics	Low volume centre	Assumed average across NHS centres	High volume centre	Source
Device lifetime (years)	5	5	5	Circassia
Use of FeNO	100% diagnosis	NA	30% diagnosis, 70% monitoring	Committee's expert opinion
No. of tests per year	100	300	450	Committee's expert opinion
Cost of device	£1,250	£1,250	£1,250	Circassia
Cost of test kits: 300	NA	£1,645	£1,645	Circassia
Cost of test kits: 100	£890	NA	NA	Circassia
Annuitisation factor for specific device lifetime [(a)]	4.67	4.67	4.67	Calculation
Annuitized mean per-test cost	**£11.57**	**£6.37**	**£6.08**	**Calculation**

Note: All prices are VAT-exclusive
(a) Calculated assuming a discounting factor of 3.5%

The test was cheapest in the scenario with a high volume and more expensive with a lower volume. In the base case scenario, a central case was assumed, reflecting the expected average across NHS centres (Table 24). This figure was also used in previous analyses in the UK(Harnan, et al., 2017).

Table 24: Cost of FeNO test

Resource	Quantity	Unit cost	Total cost	Source
FeNO test	1 test	£6.37[(a)] (£6.08 to £11.57)	£6.37 (£6.08 to £11.57)	Circassia
Time of practice nurse	15 minutes	£63.38 per hour	£15.84	PSSRU 2022(Jones, Birch, Dargan, Forder, Roland)
Total cost	**£22.21 (£21.92 to £27.41)**			

(a) The central case of £6.37 was used in the base case scenario

The cost of a skin prick test was calculated using information from a previous cost analysis conducted for NICE Food Allergy guideline CG116 (see Table 25).

Table 25: Skin prick test cost

Resource	Value	Source
Cost of vials (a)	£20	Cannon 2019(Cannon, et al., 2019) inflated to 2022
No. of drops per vial (b)	80	NICE Food Allergy CG116(National Institute for Health and Care Excellence, 2011)
Lancet (200) (c)	£13.78	MedicalWorld(Medical World)
Controls x2 (d)	£15.63	NICE Food Allergy CG116(National Institute for Health and Care Excellence, 2011)
Nurse time minutes (e)	40	NICE Food Allergy CG116(National Institute for Health and Care Excellence, 2011)
Nurse cost per hour (f)	£63.38	PSSRU 2022(Jones, Birch, Dargan, Forder, Roland)
No of allergies tested for (g)	8	NICE Food Allergy CG116(National Institute for Health and Care Excellence, 2011)
Total [(a)]	**£45**	

Note: all prices are VAT exclusive
*(a) Calculated as following: {[(a/b) + (c/200)]*g}+(d/b)+(f/60*e)*

The cost of an IgE allergy test was provided by the committee whereas the cost of collecting the cost, phlebotomy, was estimated using the NHS Reference cost. As per common practice when collecting blood from children, the cost of a local anaesthetic was included as well (see Table 26)

Table 26: Cost of total serum IgE blood test

Resource	Cost	Source – code
Allergy test	£10.92	Lothian NHS trust / Committee source.
Phlebotomy	£4.70	NHS reference costs 2021/2022 DAPS08(NHS England, 2022)

Resource	Cost	Source – code
Emla 5% cream	£0.41	BNF 2024(Joint Formulary Committee, 2024)
Total	**£16.03**	

The cost of a blood eosinophils test was sourced from the National Cost Collection 2021 – 2022 and calculated as the sum of haematology and phlebotomy (see Table 27). When administered to children, the cost of the local anaesthetic was added to the base cost.

Table 27: Cost of blood eosinophils test

Resource	Cost	Source – code
Haematology	£2.96	NHS reference costs 2021/2022 DAPS05(NHS England, 2022)
Phlebotomy	£4.70	NHS reference costs 2021/2022 DAPS08(NHS England, 2022)
Emla 5% cream	£0.41	BNF 2024(Joint Formulary Committee, 2024)
Total in adults	£7.66	
Total in children	£8.07	

The cost of bronchial challenge test was sourced from the National Cost Collection 2021 – 2022(NHS England, 2022), comprising aggregated costs across all NHS providers in England (Table 28). The code “DZ36Z” does not distinguish between a challenge test with methacholine or mannitol, so its cost was applied to both tests. Any difference is expected to be negligible as the bulk of the cost is caused by the time required from a respiratory specialist doctor.

Table 28: Cost of bronchial challenge test and blood eosinophils

Test	Cost	Source – code
Bronchial challenge test with methacholine	£179.49	National Cost Collection 2021-22 – DZ36Z(NHS England, 2022)
Bronchial challenge test with mannitol	£179.49	National Cost Collection 2021-22 – DZ36Z(NHS England, 2022)

Table 29 provides a summary of the cost of all the tests included in this analysis. Bronchial challenge test is, by far, the most expensive test available as it is conducted in a secondary care setting. The cheapest test appears to be blood eosinophils, followed by spirometry and FeNO.

Table 29: Summary of the costs of all tests

Test	Cost of consumables	Staff time required	Total cost
Spirometry	£1.8	20 minutes	£22.93
BDR	£7.47	30 minutes	£39.16
PEFv	£4.65	20 minutes [(a)]	£25.78
FeNO	£6.37	15 minutes	£22.21
Skin prick test	£2.75	40 minutes	£45
Total IgE blood test	NA	NA	£16.03
Blood eosinophils	NA	NA	Adults: £7.66

Test	Cost of consumables	Staff time required	Total cost
			Children: £8.07
Bronchial challenge test with methacholine or mannitol	NA	NA	£179.49

(a) 10 minutes tested in the scenario analysis

2.3.73 Special combinations

The committee acknowledged that there could be an economic advantage of giving specific tests in combination during the same attendance. Specifically, receiving tests in combination could require less time compared to conducting them on separate occasions, thus reducing overall costs. The committee listed a range of combinations that were expected to bring an economic advantage (see Table 30).

Table 30: Special combinations included in the model

Combination	Consumables	Staff time required	Total cost
Spirometry & FeNO	£7.88	25 minutes	£34.29
BDR & FeNO	£13.55	35 minutes	£50.52
Spirometry & BDR	£7.47 [(a)]	30 minutes	£39.16
Skin prick test & FeNO	£8.41	40 minutes	£50.66
Skin prick test & BDR	£9.80	40 minutes	£62.62
Skin prick test & Spirometry	£4.13	40 minutes	£46.38

(a) Equal to the cost of a single BDR

Combining BDR and spirometry costs the same as a “standalone” BDR since an initial spirometry is a prerequisite for the test. For the remaining combinations, the advantage consists in a reduced time for administration. With the exceptions listed, all other combinations in the model are costed as a straightforward sum of the individual test costs.

2.3.74 Asthma treatment and monitoring

The cost of treating asthma was estimated using the resource use reported in the Novel START(Beasley, Holliday, Reddel, Braithwaite, Ebmeier, Hancox, Harrison, Houghton, Oldfield, Papi, Pavord, Williams, Weatherall, Novel, 2019) with the price of each drug sourced from the British National Formulary (BNF(Joint Formulary Committee, 2024)) (see Table 31). Adults are assumed to be initiated to an ICS/LABA as-needed therapy, whereas children follow an ICS until they reach adulthood, as per recommendation.

Table 31: Cost of asthma treatment

Treatment	Drug	Actuations per day	Cost per year
ICS/LABA	Budesonide formoterol	ICS/LABA: 0.53	£45.14
ICS + SABA [(a)]	Budesonide + albuterol	ICS: 1.11 SABA: 1.01	£60.50

(a) Only applied in children in the base case scenario.

The cost of annual monitoring was estimated drawing on committee’s expert opinion as shown in Table 32. In 80% of the cases, monitoring was assumed to require an annual practice nurse visit, which increases to 2 visits in 15% of the cases. In a minority of patients, estimated by the committee to be around 5%, monitoring was assumed to require a specialist

visit. Although in the base case scenario the cost of FeNO was not factored in, a scenario analysis where each visit includes FeNO was included.

Table 32: Cost of monitoring asthma

Proportion of people	Resource per year	Cost
80%	1 practice nurse visit	£16.37
15%	2 practice nurse visits	£32.74
5%	1 outpatient visit	£185.07
0 or 100%	FeNO (high volume)	£6.08
Total cost per year (excluding FeNO) [(a)]	£58.54	
Total cost per year (including FeNO)	£65.53	

(a) Base case scenario

2.3.75 Cost of exacerbations

A different cost was applied to a mild/moderate and a severe exacerbation drawing on information provided by the committee and derived from SYGMA 2(Bateman, Reddel, O'Byrne, Barnes, Zhong, Keen, Jorup, Lamarca, Siwek-Posluszna, FitzGerald, 2018), which included detailed information on the resource use associated with a severe exacerbation.

The committee recognised that a mild or moderate exacerbation would result in a GP visit where the patient would be treated with salbutamol via a spacer (see Table 33).

Table 33: Cost of mild/moderate exacerbation

Resource	Cost	Source
GP visit	£38	PSSRU 2022(Jones, Birch, Dargan, Forder, Roland)
Salbutamol MDI plus spacer	£4	BNF(Joint Formulary Committee, 2024) and NHS Supply Chain Catalogue(NHS Supply Chain Catalogue., 2022)
Total	£42	

Abbreviations: MDI = metered dose inhaler

A severe exacerbation is a more serious event that could lead, in a few cases, to hospitalisation. The resource use associated with a severe exacerbation was derived from SYGMA 2, a double-blind randomised international trial comparing ICS/LABA to ICS + SABA (see Table 34).

Table 34: Cost of a severe exacerbation

Proportion	Resource use	Cost	Source
80%	Systemic glucocorticoid	Adults = £1.88 [(a)] Children = £0.60 [(b)]	Proportion: Sygma 2(Bateman, Reddel, O'Byrne, Barnes, Zhong, Keen, Jorup, Lamarca, Siwek-Posluszna, FitzGerald, 2018) Cost: BNF(Joint Formulary Committee, 2024)
13%	Accident & emergency	£113 [(c)]	Proportion: Sygma 2(Bateman, Reddel,

Proportion	Resource use	Cost	Source
			O'Byrne, Barnes, Zhong, Keen, Jorup, Lamarca, Siwek-Posluszna, FitzGerald, 2018) Cost: National Cost Collection 2021/22(NHS England, 2022)
7%	Hospitalisation	Adults: £1,181 (d) Children: £ 1223 (d)	Proportion: Sygma 2(Bateman, Reddel, O'Byrne, Barnes, Zhong, Keen, Jorup, Lamarca, Siwek-Posluszna, FitzGerald, 2018) Cost: National Cost Collection 2021/22(NHS England, 2022)
Average cost	£102		

(a) 8 tablets of prednisolone 5mg a day for 7 days
(b) 6 tables of prednisolone 5 mg a day for 3 days
(c) Weighted average of emergency non-admitted episodes
(d) Weighted average of codes of asthma with and without interventi8on

In addition to the costs illustrated in Table 34, a severe exacerbation was assumed to require an initial GP visit and a further GP or nurse visit for follow-up (a 50% ratio was assumed). The committee also acknowledged that people who were hospitalised would need to return to the hospital for a follow-up control visit, so the cost of an additional consultant-led follow up appointment was added.

2.40 Computations

The model was constructed in R studio (Build 402) and Shiny and was evaluated by cohort simulation. Time dependency was built in by cross referencing the cohorts age as a respective risk factor for mortality. Baseline utility and time-to-first exacerbation were also time dependent and was conditional on the number of years after entry to the model.

People enter the model in cycle 0 in one of the following four states: true positive, true negative, false positive or false negative states. Only in analyses on children, people in the true positive or false negative states can move to the remission state using transition probabilities derived by the survival curves shown in Figure 13, Figure 14 and Figure 15. In addition, people in the false negative state can move to the true positive state after a correct diagnosis using transition probabilities derived from the survival curve in Figure 11. People with a false positive diagnosis can move to the true negative using the survival curve shown in Figure 16. Finally, all people can move to the dead state with transition probabilities calculated using ONS life tables and hazard ratios and excess mortality estimated in a population with asthma.

All rates were converted into transition probabilities for the respective cycle length: 1 month in the short-term Markov model 1 year in the long-term model. The above conversions were done using the following formulae:

$Selected\ rate\ (r) = \frac{-\ln(1-P)}{t}$	Where *P*=probability of event over time *t*

	t=time over which probability occurs (1 month or 1 year)
$Transition\ Probability\ (P) = 1 - e^{-rt}$	Where *r*=selected rate *t*=cycle length (1 month or 1 year)

Life years for the cohort were computed each cycle. To calculate QALYs for each cycle, Q(t), the time spent in the alive state of the model was weighted by a utility value that is dependent on the time spent in the model and the proportion of people in each state. A half-cycle correction was applied. QALYs were then discounted to reflect time preference (discount rate 3.5%). QALYs during the first cycle were not discounted. The total discounted QALYs were the sum of the discounted QALYs per cycle. The total discounted QALYs were the sum of the discounted QALYs per cycle.

Costs per cycle, C(t), were calculated in the same way as QALYs. Costs of diagnostic tests were applied in the first cycles and not discounted. Costs occurring later were discounted to reflect time preference (discount rate 3.5%) in the same way as QALYs using the following formula:

Discounting formula:

$\text{Discounted total} = \frac{\text{Total}}{(1+r)^n}$	Where: *r*=discount rate per annum *n*=time (years)

The total cost and QALYs accrued by the cohort was divided by the number of patients in the population to calculate a cost per patient and cost per QALY.

2.55 Sensitivity analyses

Various scenario analyses were conducted to test the robustness of the results of the model. Table 35**Error! Reference source not found.** describes the different scenario analyses where the light blue colour indicates the scenarios adopted in the base case scenario.

Table 35: Scenario analyses

Feature	Scenario	Description
Prevalence of asthma	Prevalence from RADicA	Use the prevalence of people in RADicA study
	High prevalence of asthma	Set the prevalence of asthma to 80%
	Low prevalence of asthma	Set the prevalence of asthma to 40%
Specificity of FeNO in adults	RADicA	Use the specificity of FeNO (>50 ppb) observed in RADicA
	Threshold analysis	Test different values of specificity for FeNO ranging from 0.9 to 1
Allergy tests in children	Skin prick test	Assume that the available allergy test in children is skin prick test
	IgE blood test	Assume that the available allergy test in children is IgE blood test
Maximum time spent with a false negative diagnosis	1 year	Assume that all false negative diagnoses are resolved within 1 year
	2 years	Assume that all false negative diagnoses are resolved within 2 years
	5 years	Assume that all false negative diagnoses are resolved within 5 years

Feature	Scenario	Description
Time-to-first exacerbation parametric curve	Exponential	Use an exponential parametric curve to estimate time to first exacerbation
	Log-logistic	Use a log-logistic parametric curve to estimate time to first exacerbation
Quality of life of people with untreated asthma	Uncontrolled asthma	Assume that people with untreated asthma share the quality of life of those with uncontrolled asthma
	General population with asthma	Assume that people with untreated asthma share the quality of life the general population with asthma
Nation setting	England	Run the analysis using England's unit costs and life expectancy
	Scotland	Run the analysis using Scotland's unit costs and life expectancy
Healthcare professional conducting diagnostic tests	Practice nurse	Assume that all tests, excluding those conducted in secondary tests, are administered by a practice nurse
	GP	Assume that all tests, excluding those conducted in secondary tests, are administered by a GP
Time required for a PEFv	20 minutes	Assume that 20 minutes are necessary for explaining and interpreting PEFv results
	10 minutes	Assume that 10 minutes are necessary for explaining and interpreting PEFv results
Volume of FeNO activity in the centre	Low activity	Use the cost of FeNO estimated for centres with low activity
	Medium activity	Use the cost of FeNO estimated for centres with medium activity
	High activity	Use the cost of FeNO estimated for centres with high activity
FeNO in monitoring visits	FeNO not included	Assume that FeNO is not administered in asthma monitoring visits
	FeNO included	Assume that FeNO is administered in asthma monitoring visits
Initial treatment	ICS/LABA	Assume that the initial treatment for asthma is the combination inhaler ICS/SABA PRN
	ICS + SABA	Assume that the initial treatment for asthma is maintenance ICS and SABA PRN
Formulation of prednisolone in children	Normal tablets	Assume that children receive normal tablets of prednisolone during exacerbations
	Soluble tablets	Assume that children receive soluble tablets of prednisolone during exacerbations

2.5.11 Prevalence of asthma

In the base case scenario, the prevalence of asthma among those reporting respiratory symptoms suggestive of asthma was estimated from RADicA.

The committee acknowledged that an important factor considered by clinicians when reaching a diagnosis or considering additional testing is clinical history. People who had a history of asthma attacks and, therefore, are very likely to have asthma, may be easier to diagnose and require less tests whereas those with unspecific symptoms and no clear

clinical history might need additional testing to reach a diagnosis. Therefore, two separate scenario analyses were explored where prevalence was set at 80% and 40% for a cohort with, respectively, high and low probability of asthma.

2.5.2 FeNO threshold analysis in adults

In the base case scenario, specificity of FeNO in adults was estimated using RADicA alone. As there is uncertainty in the published literature regarding the performance of FeNO at high cut-off values (40 – 50 ppv), a threshold analysis was conducted where values between 0.9 and 1 were systematically tested.

2.5.3 Allergic test in children

In the base case scenario, skin prick test was assumed to be the standard allergy test available for children with suspected asthma. The committee acknowledged that the availability of skin prick tests is limited nationwide, primarily due to a lack of training and disparities in healthcare access. A potential cost-effective alternative, is the IgE test, an allergen-specific immunoglobulin E test that measures the level of antibodies the immune system makes to protect the bodies from allergens. A further advantage of IgE is that, when conducted alongside blood eosinophils (strategy 3 in children), it does not require a further blood sample as the same sample can be used for both tests. Skin prick test and IgE were assumed to be perfectly correlated, so they could not be included in the same scenario. Therefore, a separate scenario with IgE instead of skin prick test was explored in the sensitivity analysis, which also incorporates potential savings arising from conducting multiple blood test using a single sample.

2.5.4 Maximum time spent with a false negative diagnosis

In the base case scenario it was assumed that a person could not spend more than two years with a false negative diagnosis and untreated asthma. Two scenarios were tested in the sensitivity analysis: one with a shorter maximum time of one year, and a second with a longer maximum time duration of five years.

2.5.5 Parametric curve for time-to-first exacerbation

The survival analysis based on the pseudo individual-patient data on time-to-first exacerbation revealed that two parametric curves provided the best fit for the data: an exponential parametric curve exhibiting the lowest BIC and a log-logistic curve exhibiting the lowest AIC. The exponential curve was ultimately chosen in the base case scenario as its long-term predictions were considered more realistic. The consequences of using a log-logistic curve for long-term extrapolation were explored in the scenario analysis.

2.5.6 Quality of life of people with untreated asthma

In the base case scenario, it was assumed that people with untreated asthma shares the quality of life of those whose asthma is uncontrolled. However, the committee acknowledged that, sometimes, people may remain undiagnosed because their asthma is mild or intermitted. In such cases, it is unrealistic to assume that their quality of life would be the same of those with uncontrolled symptoms of asthma. Therefore, a scenario analysis was included that assumes that people with untreated asthma would share the quality of life of the general population with asthma, which includes both people with controlled and uncontrolled asthma.

2.5.7 Nation setting

The base case scenario was conducted from an England's perspective and uses England-specific healthcare unit costs and life expectancy. As the guideline is a joint project between NICE, BTS (British Thoracic Society) and SIGN (Scottish Intercollegiate Guidelines Network), the committee agreed it was appropriate to include a scenario more reflective of Scotland's particular settings. In this scenario, Scotland-specific life tables(Office for National Statistics, 2021) were used to estimate life expectancy and the unit costs of healthcare staff were adjusted to reflect NHS Scotland pay scales(British Medical Association, 2024).

2.5.8 Healthcare professionals

In the base case scenario it is assumed that a practice nurse would explain, administer, and interpret all the diagnostic tests with the exception of bronchial challenge tests (with mannitol or methacholine), which are always assumed to be conducted in secondary care. A scenario analysis was conducted where tests are provided by GPs instead.

2.5.9 Healthcare staff time needed for a PEFv

While patients collect PEFv measurements independently, healthcare professionals, such as nurses or GPs, are essential for explaining the test, performing calculations, and interpreting the results. The committee estimated this involvement to take approximately 20 minutes. However, it is possible that this time could be lower if the healthcare professionals already have experience in interpreting the results. Hence, a sensitivity analysis accounting for a reduced time of 10 minutes was also included.

2.5.10 Volume of FeNO

As reported in Table 23, three different estimations of the per-test cost of FeNO were calculated reflecting three centres with different volumes of FeNO tests delivered. In the base case scenario, the central estimation was used, as it is expected to reflect the average across NHS centres. In the scenario analyses, both the low and higher cases were explored.

2.5.11 FeNO in monitoring visit

The base case scenario assumes that an average asthma review visit does not involve a FeNO measurement. As this might change in the future following the new recommendations drafted for FeNO for monitoring, a scenario where every annual review requires FeNO testing was included in the sensitivity analysis.

2.5.12 Initial treatment in adults

In the base case scenario, the initial treatment for adults who are diagnosed with asthma is assumed to be ICS/LABA, reflecting the new recommendations on initial treatment. A scenario where people are initiated to the previously recommended treatment, ICS + SABA, was added where costs and exacerbation rates were adjusted accordingly.

2.5.13 Formulation of prednisolone in children

Children might have troubles swallowing standard tablets of prednisolone during exacerbations. In practice these are often crushed and dissolved in the water when dispensed to children. Nevertheless, a soluble formulation is available but considerably more expensive (around 60 times more). A sensitivity analysis was conducted where children receive soluble tablets instead, to explore whether the higher cost would have any significant impact on the model results.

2.6 Model validation

The model was developed in consultation with the committee. Model structure, inputs and results were presented to and discussed with the committee for clinical validation and interpretation.

The model was systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that results were plausible given inputs. The model was peer reviewed by the NICE Guidelines Technical Support Unit (TSU) at the university of Bristol. The review included assessing the structure, presentation and settings, investigating data sources and model input calculations, evaluating the functionality, testing the correctness of the Markov traces and checking the sensitivity analyses.

2.7 Estimation of cost effectiveness

The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with 2 alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold the result is considered to be cost effective. If both costs are lower and QALYs are higher the option is said to dominate and an ICER is not calculated.

$$ICER = \frac{Costs(B) - Costs(A)}{QALYs(B) - QALYs(A)}$$

Where: Costs(A) = total costs for option A; QALYs(A) = total QALYs for option A

Cost effective if:
- ICER < Threshold

It is also possible, for a particular cost-effectiveness threshold, to re-express cost-effectiveness results in term of net health benefit (NHB). This is calculated as a difference between total QALY and total cost divided by the threshold cost per QALY values (£20,000). The decision rule then applied is that the comparator with the highest NHB is the cost-effective option at the specified threshold. That is the option that provides the highest number of QALYs at an acceptable cost.

$$Net\ Health\ Benefit(X) = \left(QALYs(X)\right) - Costs(X) / \lambda$$

Where: λ = threshold (£20,000 per QALY gained)

Cost effective if:
- Highest net benefit

Both methods of determining cost effectiveness will identify exactly the same optimal strategy. For ease of computation NHB is used in this analysis to identify the optimal strategy.

2.8 Interpreting results

NICE sets out the principles that committees should consider when judging whether an intervention offers good value for money.(National Institute for Health and Care Excellence, National Institute for Health and Clinical Excellence) In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- The intervention costs less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

As several diagnostic strategies were compared, NHBs were used to rank the strategies on the basis of their relative cost effectiveness. The highest NHB identifies the optimal strategy at a willingness to pay of £20,000 per QALY gained.

3 Results

The analysis was conducted separately for adults and children with different strategies explored in each population. In the following section, probabilistic and deterministic results in adults and children are presented.

3.1 Adults model

3.1.1 Base case probabilistic results

Table 36 shows the sensitivity and specificity values associated with each strategy in adults. The last column shows the proportion of the cohort reaching the last stage of the algorithm where a bronchial challenge test with methacholine is required.

Table 36: Accuracy of diagnostic strategies[(a)] in adults

Strategy	Sensitivity	Specificity	Proportion of people requiring BCT
1	0.88 (0.78 - 0.94)	0.98 (0.88 - 1)	62.61%
2	0.84 (0.74 - 0.91)	0.87 (0.74 - 0.94)	53.39%
3	0.78 (0.66 - 0.87)	0.97 (0.86 - 1)	69.79%
4	0.91 (0.82 - 0.96)	0.86 (0.73 - 0.94)	49.57%
5	0.91 (0.82 - 0.96)	0.86 (0.73 - 0.94)	49.57%
6	0.68 (0.55 - 0.78)	0.98 (0.89 - 1)	17.43%
7	0.91 (0.82 - 0.96)	0.86 (0.73 - 0.94)	49.57%
8	0.85 (0.73 - 0.92)	0.83 (0.68 - 0.92)	52.08%
9	0.91 (0.82 - 0.96)	0.86 (0.73 - 0.94)	49.14%
10	0.86 (0.75 - 0.93)	0.94 (0.81 - 0.98)	62.37%

(a) See Diagnostic strategies in adultsTable 1 for a detailed description of the strategies

Strategy 1, 3 and 6 showed the best specificity. This is because all three strategies included the best specific tests available, BDR, PEFv and blood eosinoiphils, as well as a BCT with methacholine for people who could not be ruled in. Strategy 4, 5, 7 and 9 showed the best sensitivity as they included FeNO, which tends to increase the sensitivity of a strategy while reducing its specificity. Although most strategies require testing a significant number of people through a bronchial challenge, strategies with more than 3 tests, despite introducing complexity, ultimately reduce the proportion of people reaching the last step.

Table 37 shows the probabilistic results in the base case scenario for adults.

Table 37: Probabilistic cost-effectiveness results in adults – base case

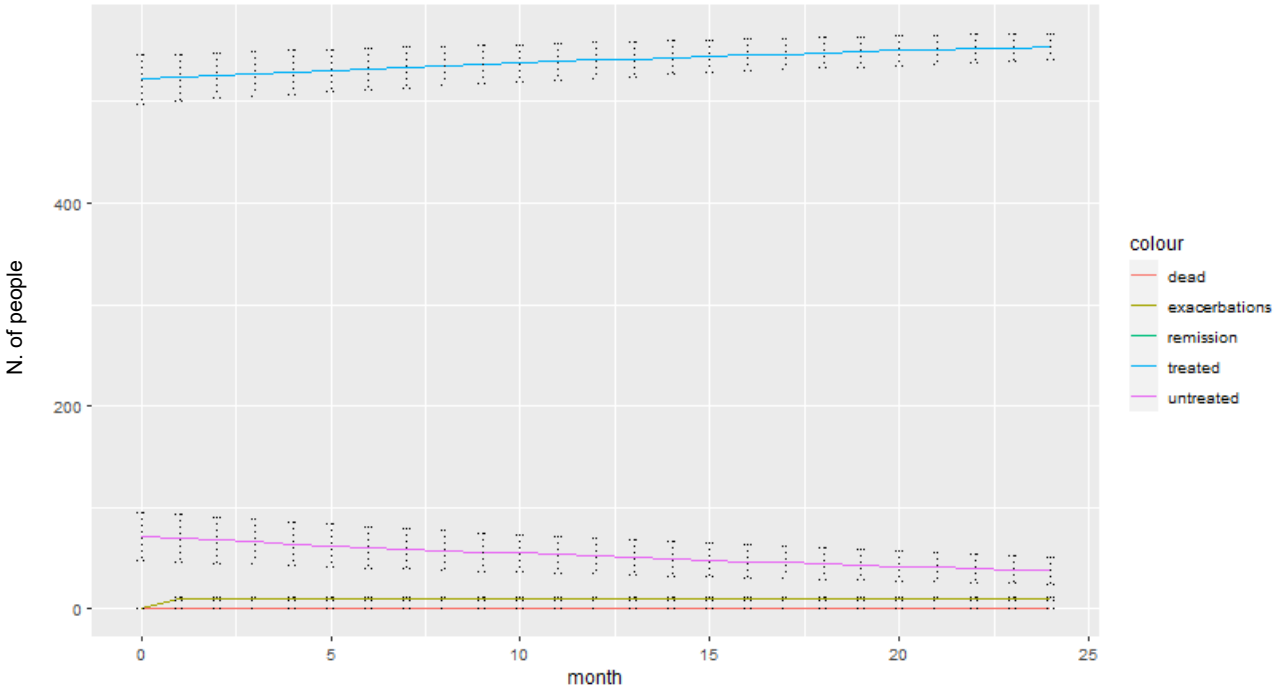
Strategy	Cost per patient	QALY per patient	Net Health Benefits	Rank	% cost-effective at 20k
1	1409 (1317 - 1501)	19.03 (16.98 - 21.08)	18.955 (18.78 - 19.13)	1	88.02%
2	1432 (1338 - 1526)	18.98 (16.93 - 21.03)	18.91 (18.732 - 19.088)	5	0%
3	1451 (1359 - 1543)	19.02 (16.97 - 21.07)	18.946 (18.772 - 19.12)	3	3.33%
4	1429 (1332 - 1526)	18.98 (16.93 - 21.03)	18.909 (18.726 - 19.092)	6	0%
5	1425 (1327 - 1523)	18.98 (16.93 - 21.03)	18.909 (18.727 - 19.091)	6	0.01%
6	1355 (1264 - 1446)	19.02 (16.97 - 21.07)	18.948 (18.774 - 19.122)	2	7.99%
7	1425 (1327 - 1523)	18.98 (16.93 - 21.03)	18.91 (18.727 - 19.093)	5	0%

Strategy	Cost per patient	QALY per patient	Net Health Benefits	Rank	% cost-effective at 20k
8	1462 (1366 - 1558)	18.97 (16.92 - 21.02)	18.896 (18.715 - 19.077)	7	0%
9	1430 (1333 - 1527)	18.98 (16.93 - 21.03)	18.91 (18.727 - 19.093)	5	0.01%
10	1444 (1351 - 1537)	19.01 (16.96 - 21.06)	18.939 (18.763 - 19.115)	4	0.64%

Strategy 1, including blood eosinophils, BDR and methacholine was the most cost-effective strategy in 88% of the simulations and the one associated with the highest health outcome. Strategy 6 was the cheapest strategy, due to its lowest use of methacholine, and the most cost-effective strategy in 8% of the simulations. Strategy 3, which was similar to strategy 1 except having PEFv instead of blood eosinophils, was the third most cost-effective strategy and ranked first in 3% of the simulations. All the remaining strategies were unlikely to be cost-effective.

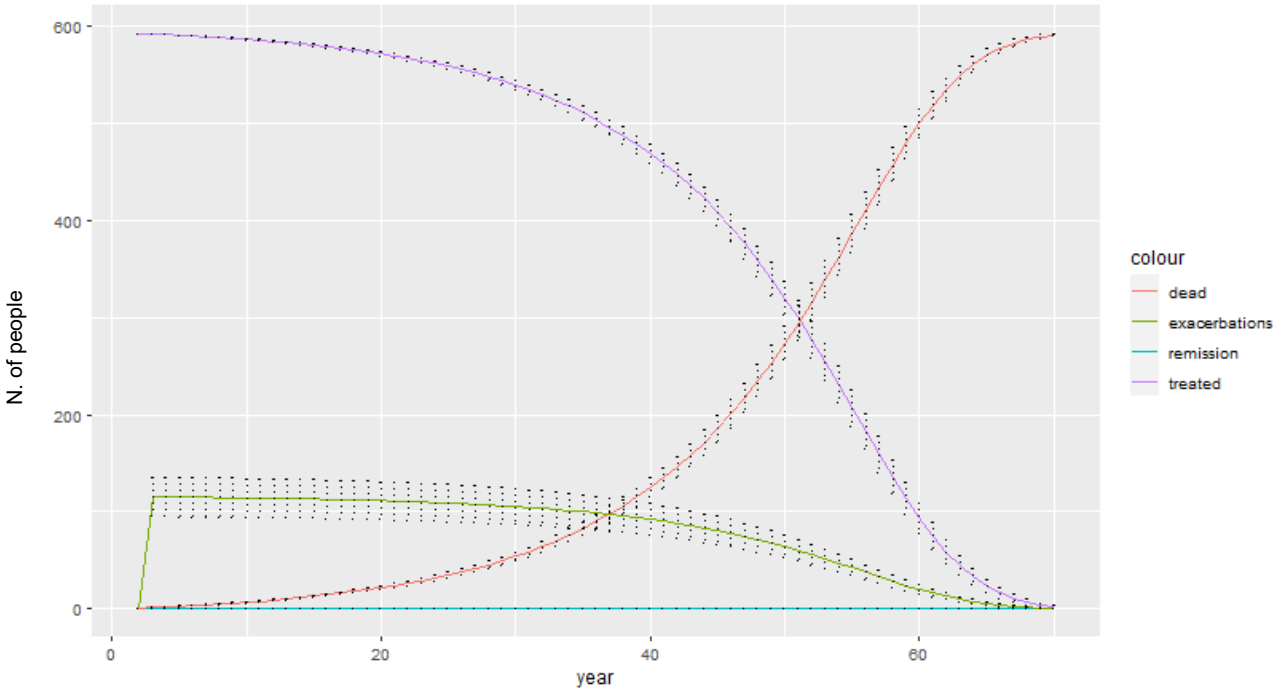
Figure 18, Figure 19, and Figure **20** show the dynamic transition of people between different states in the three model when strategy 1 is adopted. Exacerbations do not represent a separate state but capture the number of exacerbations occurring during each cycle.

Figure 18: Adults with asthma – short-term



Note: exacerbations do not represent a distinct Markov state but the number of exacerbation events occurring during each cycle

Figure 19: Adults with asthma – long-term



Note: exacerbations do not represent a distinct Markov state but the number of exacerbation events occurring during each cycle

Figure 20: Adults without asthma

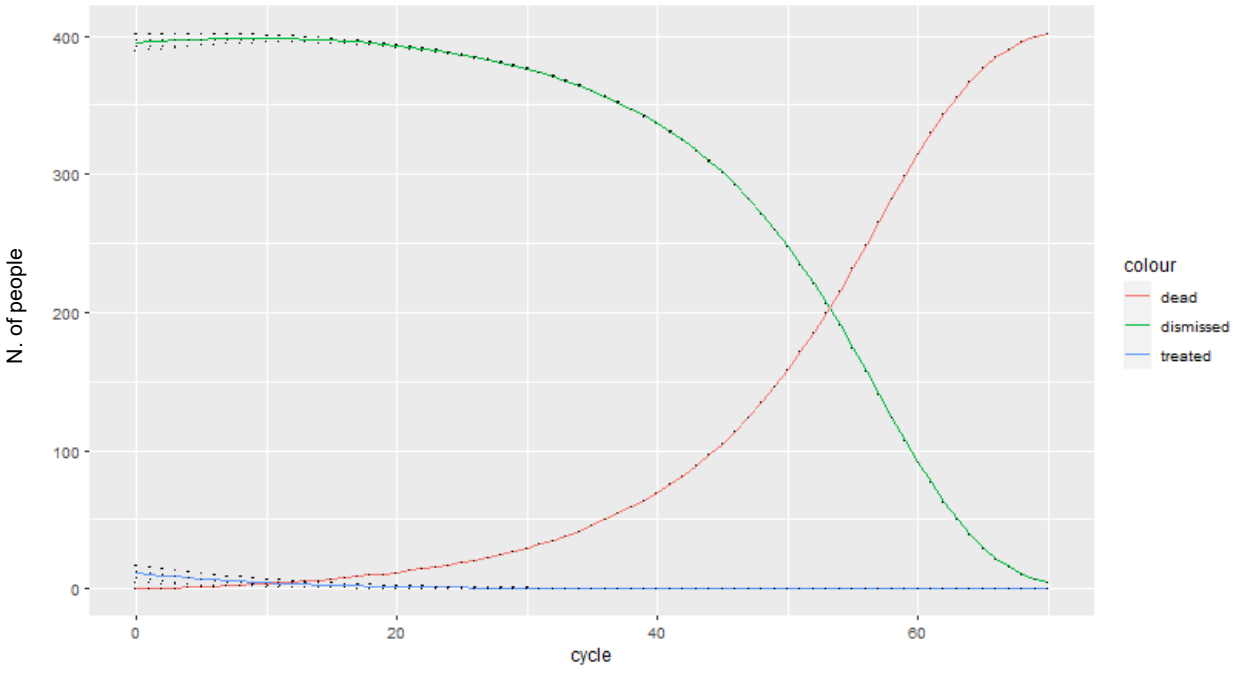


Table 38 illustrated a breakdown of costs in each strategy. As anticipated, strategy 6 is associated with the lowest cost in terms of initial tests, but it has poor sensitivity and requires more tests downstream to correct the high number of false positives. Cost of asthma monitoring and treatment tend to be higher in strategies with lower specificity as these are associated with a higher number of false positives receiving treatment and monitoring despite not having the disease. Finally, the cost associated with exacerbations is similar across the different strategies, as those with untreated asthma and higher risk of

exacerbation are assumed to be correctly diagnosed and receive the appropriate treatment once they experience the first exacerbation.

Table 38: Breakdown of costs – Adults probabilistic base case

S.	Diagnostic sequence	Other diagnostic[a]	Asthma treatment	Asthma monitoring	Exacerbation	Total
1	151 (135 - 167)	15 (6 - 24)	657 (644 - 670)	377 (370 - 384)	208 (119 - 297)	1409 (1317 - 1501)
2	143 (127 - 159)	19 (9 - 29)	674 (653 - 695)	387 (375 - 399)	209 (120 - 298)	1432 (1338 - 1526)
3	186 (170 - 202)	27 (14 - 40)	654 (641 - 667)	375 (368 - 382)	209 (121 - 297)	1451 (1359 - 1543)
4	142 (125 - 159)	11 (3 - 19)	679 (653 - 705)	390 (375 - 405)	208 (119 - 297)	1429 (1332 - 1526)
5	137 (120 - 154)	11 (3 - 19)	679 (653 - 705)	390 (375 - 405)	208 (119 - 297)	1425 (1327 - 1523)
6	85 (72 - 98)	39 (25 - 53)	649 (637 - 661)	372 (365 - 379)	211 (123 - 299)	1355 (1264 - 1446)
7	137 (120 - 154)	11 (3 - 19)	679 (653 - 705)	390 (375 - 405)	208 (119 - 297)	1425 (1327 - 1523)
8	165 (147 - 183)	18 (7 - 29)	680 (655 - 705)	390 (376 - 404)	209 (120 - 298)	1462 (1366 - 1558)
9	143 (127 - 159)	11 (3 - 19)	679 (653 - 705)	390 (375 - 405)	208 (119 - 297)	1430 (1333 - 1527)
10	176 (158 - 194)	17 (6 - 28)	663 (647 - 679)	380 (371 - 389)	209 (120 - 298)	1444 (1351 - 1537)

(a) Costs of further diagnostic exams to correct wrong diagnoses

3.1.2 Scenario analyses

Table 39 illustrates the probabilistic results of the scenario analyses. The number of the strategies ranked first, second, or third are reported with their probability of being the most cost-effective in parentheses. The ranks found in the base case is unchanged in most scenarios with a few exceptions. When there is a high probability of asthma (prevalence = 80%), strategy 6, which has a poor sensitivity, become less cost-effective. The same occurs when the maximum time spent with a false positive diagnosis is increased to 5 years, as this makes a false positive diagnosis more harmful. By contrast, when the model assumes that untreated asthma does not cause any additional harm, cheaper strategies with poor sensitivity, like strategy 6, becomes the more likely to be cost-effective (65%).

Table 39: Probabilistic scenario analyses – Adults

Scenario	1st ranked	2nd ranked	3rd ranked
Base case	Strategy 1 (88%)	Strategy 6 (8%)	Strategy 3 (3%)
High prevalence of asthma (80%)	Strategy 1 (96%)	Strategies 3 & 10 (2%)	Strategy 6 (1%)
Low prevalence of asthma (40%)	Strategy 1 (59%)	Strategy 6 (36%)	Strategy 3 (5%)
Maximum 1 year with a false negative diagnosis	Strategy 1 (72%)	Strategy 6 (24%)	Strategy 3 (4%)
Maximum 5 years with a false negative diagnosis	Strategy 1 (95%)	Strategy 3 (2%)	Strategy 6 (2%)

Scenario	1st ranked	2nd ranked	3rd ranked
Log-logistic instead of exponential for time-to-first exacerbation	Strategy 1 (92%)	Strategy 6 (5%)	Strategy 3 (3%)
No QoL reduction in people with untreated asthma	Strategy 6 (65%)	Strategy 1 (31%)	Strategy 3 (4%)
Scotland settings	Strategy 1 (88%)	Strategy 6 (8%)	Strategy 3 (3%)
GP conduct diagnostic tests	Strategy 1 (92%)	Strategy 6 (7%)	Strategy 3 (1%)
10 minutes required for PEFv	Strategy 1 (87%)	Strategy 6 (8%)	Strategy 3 (4%)
Low FeNO activity	Strategy 1 (88%)	Strategy 6 (7%)	Strategy 3 (3%)
High FeNO activity	Strategy 1 (88%)	Strategy 6 (8%)	Strategy 3 (3%)
FeNO included in all monitoring visits	Strategy 1 (88%)	Strategy 6 (8%)	Strategy 3 (3%)
ICS + SABA as treatment in adults	Strategy 1 (88%)	Strategy 6 (8%)	Strategy 3 (3%)

3.1.8 FeNO specificity threshold analysis

In the base case scenario in adults, sensitivity and specificity of all tests were estimated using the IPD from RADicA study. Diagnostic accuracy in RADicA generally aligned well with the committee's expectations (see 2.3.2.1). However, the committee noted that there was heterogeneity in the specificity of FeNO reported in the literature, with some studies(Schneider, Brunn, Hapfelmeier, Schultz, Kellerer, Jorres, 2022, Schneider, et al., 2015) reporting a higher specificity at cut-offs close to 50ppb. Therefore, a sensitivity analysis was conducted where the specificity of FeNO was allowed to vary to determine the threshold value that would make a strategy with FeNO as initial test cost-effective. Although specificity and sensitivity are inversely correlated, it is noteworthy that sensitivity was held constant in the threshold analysis. Therefore, caution is advised when interpreting the results.

For this analysis, only two strategies were considered: strategy 1, that was the most cost-effective in the base case scenario, and strategy 2, which was similar but used FeNO instead of blood eosinophils in the first step (see Table 40).

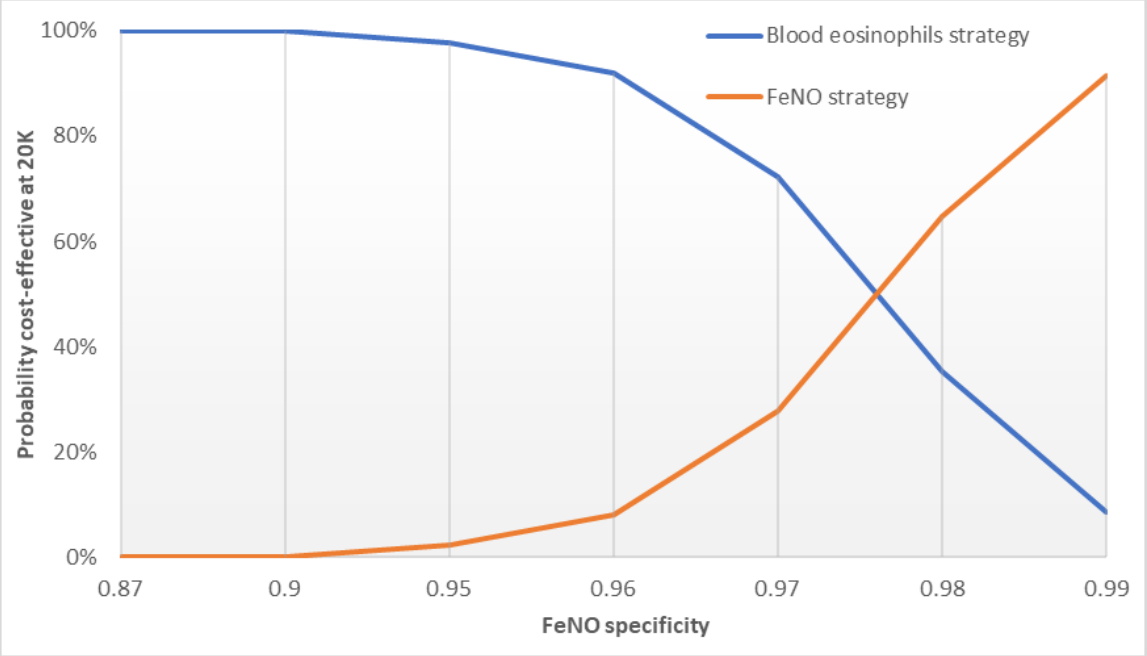
Table 40: Diagnostic strategies included in FeNO threshold analysis

S	1st step	2nd step	3rd step	4th step
1	Blood Eosinophils	+: Diagnose asthma -: BDR	+: Diagnose asthma -: Methacholine	–
2	FeNO	+: Diagnose asthma -: BDR	+: Diagnose asthma -: Methacholine	–

Abbreviations: BDR: bronchodilator reversibility; FeNO: Fractional exhaled nitric oxide

Figure 21 shows the results of the threshold analysis, with the vertical axis indicating the likelihood that a particular strategy is cost-effective and the horizontal axis reporting the level of specificity of FeNO. Not surprisingly, the probability of FeNO strategy being the most cost-effective increases in tandem with the increase of FeNO specificity. When FeNO specificity reaches 0.98, which is equal to the specificity estimated for blood eosinophil, FeNO strategy becomes more likely to be cost-effective.

Figure 21: FeNO specificity threshold analysis



This implies that FeNO is a cost-effective test at the beginning of a diagnostic algorithm only if its specificity at the recommended cut-off is comparable or superior to that of other highly specific tests such as PEFv or blood eosinophils. Otherwise, if its specificity is lower, there is a risk of over diagnosing asthma in the initial step of the sequence, leading to potential resource wastage for the NHS.

3.2 Children model

3.2.1 Base case probabilistic results

Table 41Table 36 shows the sensitivity and specificity values associated with each strategy in children. The last columns shows the proportion of the cohort reaching the last stage of the algorithm where a bronchial challenge test with methacholine is administered.

Table 41: Accuracy of diagnostic strategies[(a)] in children

Strategy	Sensitivity	Specificity	Proportion of people requiring BCT
1	0.78 (0.77 - 0.79)	0.92 (0.92 - 0.93)	39.58%
2	0.77 (0.76 - 0.77)	0.87 (0.87 - 0.88)	32.31%
3	0.88 (0.87 - 0.88)	0.67 (0.66 - 0.68)	31.03%
4	0.83 (0.82 - 0.84)	0.84 (0.84 - 0.85)	37.82%
5	0.79 (0.78 - 0.8)	0.87 (0.86 - 0.87)	34.36%
6	0.8 (0.79 - 0.81)	0.91 (0.9 - 0.91)	26.89%
7	0.88 (0.87 - 0.89)	0.67 (0.66 - 0.68)	34.36%
8	0.84 (0.83 - 0.85)	0.84 (0.83 - 0.85)	63.38%
9	0.79 (0.78 - 0.8)	0.87 (0.86 - 0.87)	30.09%
10	0.95 (0.95 - 0.96)	0.56 (0.55 - 0.57)	34.37%

(a) See Diagnostic strategies in adultsTable 2 for a detailed description of the strategies

Strategies 1, 3 and 5 and 6 reached the best specificity whereas strategies 8 had the best sensitivity. Overall, compared to adults, all diagnostic strategies in children require fewer bronchial challenge tests as a rule-in-rule-out approach is more effective in reducing the number of people reaching the last step of the diagnostic pathway.

Table 42 illustrates the probabilistic results in the base case scenario for children.

Table 42: Probabilistic cost-effectiveness results in children – base case

Strategy	Cost per patient	QALY per patient	Net Health Benefits	Rank	% cost-effective at 20k
1	1076 (958 - 1194)	23.14 (21.09 - 25.19)	23.085 (22.913 - 23.257)	1	46.38%
2	1125 (1007 - 1243)	23.13 (21.08 - 25.18)	23.069 (22.895 - 23.243)	5	0%
3	1114 (995 - 1233)	23.1 (21.05 - 25.15)	23.043 (22.86 - 23.226)	6	0%
4	1074 (956 - 1192)	23.13 (21.08 - 25.18)	23.075 (22.899 - 23.251)	3	2.66%
5	1111 (993 - 1229)	23.13 (21.08 - 25.18)	23.072 (22.898 - 23.246)	4	0.15%
6	1067 (949 - 1185)	23.14 (21.09 - 25.19)	23.084 (22.911 - 23.257)	1	46.88%
7	1125 (1006 - 1244)	23.1 (21.05 - 25.15)	23.042 (22.858 - 23.226)	7	0%
8	1081 (963 - 1199)	23.13 (21.08 - 25.18)	23.076 (22.9 - 23.252)	2	3.75%
9	1107 (989 - 1225)	23.13 (21.08 - 25.18)	23.072 (22.898 - 23.246)	4	0.18%
10	1178 (1057 - 1299)	23.09 (21.03 - 25.15)	23.027 (22.837 - 23.217)	8	0%

Strategies 1 and 6 were the most cost-effective strategies in more than 90% of the simulations. Both were similar, involving an initial FeNO followed by a skin prick test or IgE for those who tested negative. However, strategy 6 included an additional step with blood eosinophils before referring children to bronchial challenge test with methacholine, to reduce the proportion of children needing secondary care (see Table 43). The committee acknowledged that strategy 6 could be particularly useful when children undergo IgE testing in step 2. This is because the blood collected in step 2 could be used to conduct IgE and blood eosinophils simultaneously, without the need of further blood sampling.

Table 43: Most cost-effective strategies in children

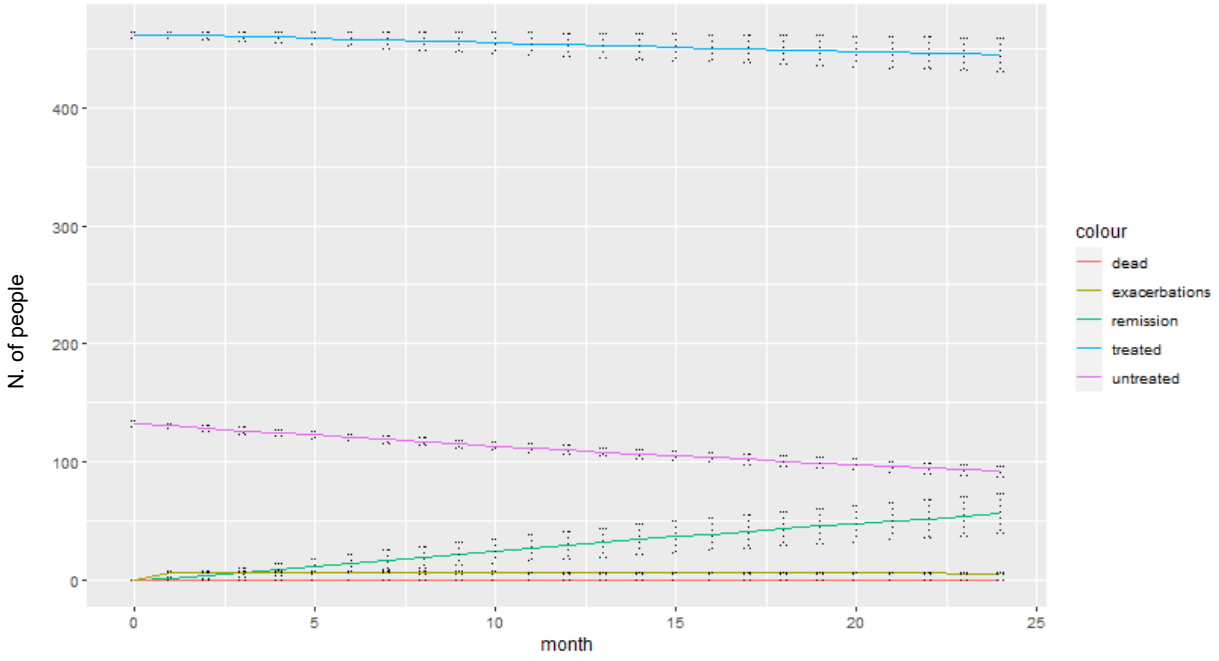
S	1st step	2nd step	3rd step	4th step
1	FeNO	+: Diagnose asthma -: SPT/IgE	+: Methacholine -: Exclude asthma	–
3	FeNO	+: Diagnose asthma -: SPT/IgE	+: Blood eosinophils -: Exclude asthma	+: Diagnose asthma -: Methacholine

All first three cost-effective strategies include FeNO in the first step. This is because FeNO was found to be highly specific in children and is relatively cheap. The third most cost-effective strategy starts with blood eosinophils, another highly specific and affordable test. BDR was also found to be highly specific, but it is more expensive and so it became the third most cost-effective initial test after FeNO and blood eosinophils. PEFv is another cheap alternative but was found to be particularly inaccurate in children, so it is the least cost-effective test to be offered at the beginning of a sequence.

Figure 22, Figure 23 and Note: *exacerbations do not represent a distinct Markov state but the number of exacerbation events occurring during each cycle*

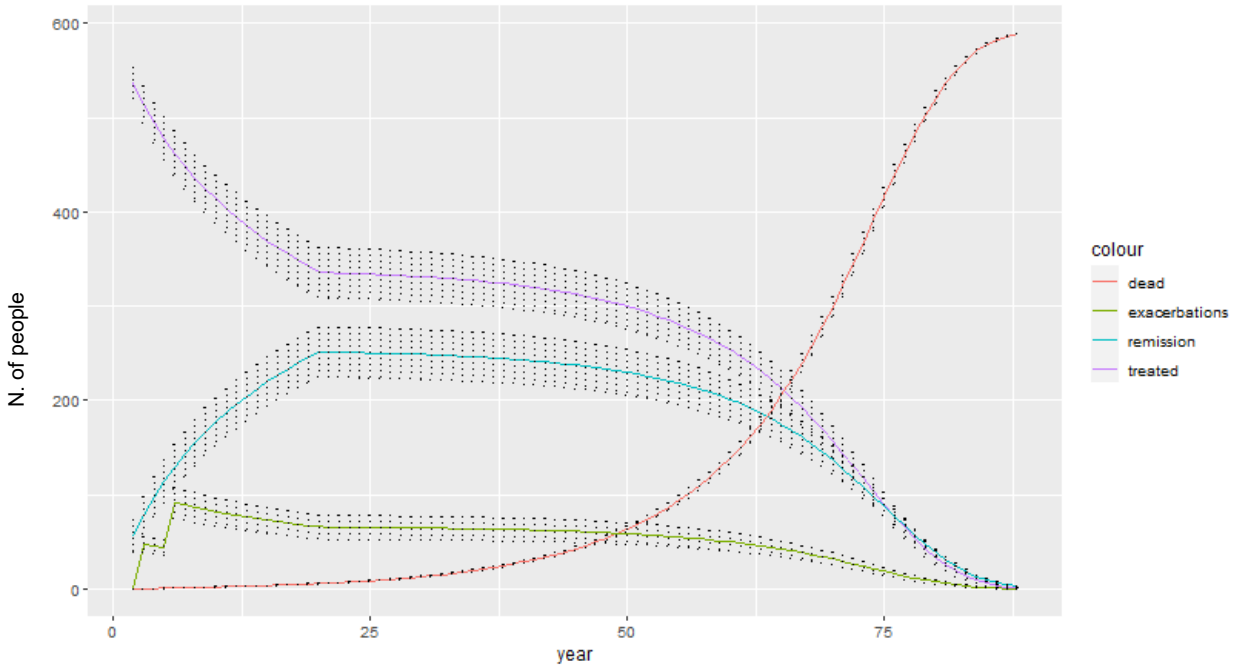
Figure 24 show the dynamic transition of children between different states in the three model when strategy 1 is adopted. Differently from the adults, children with asthma can achieve remission, which is treated as a separate health state. Exacerbations do not represent a separate state but capture the number of exacerbations occurring during each cycle.

Figure 22: Children with asthma – short-term



Note: exacerbations do not represent a distinct Markov state but the number of exacerbation events occurring during each cycle

Figure 23: Children with asthma – long-term



Note: exacerbations do not represent a distinct Markov state but the number of exacerbation events occurring during each cycle

Figure 24: Children without asthma

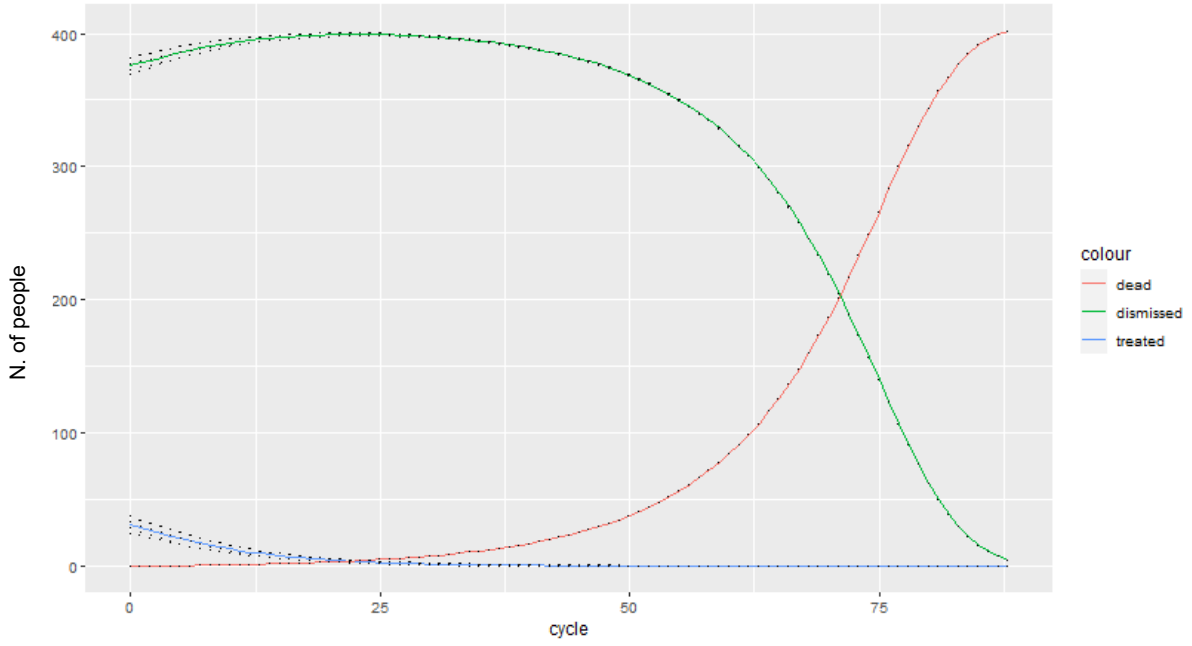


Table 44 presents a breakdown of lifetime costs across the different strategies. The overall cost of the tests included in the diagnostic sequence tend to be lower in strategy with a lower need of methacholine. Compared to adults, lifetime asthma management, monitoring and

exacerbation costs are lower as many who are diagnosed with asthma during childhood achieve remission during their lifetime (see section 2.3.3.2 and Figure 23).

Table 44: Breakdown of costs – Children probabilistic base case

S.	Diagnostic sequence	Other diagnostic[a]	Asthma treatment	Asthma monitoring	Exacerbation	Total
1	131 (130 - 132)	33 (30 - 36)	488 (435 - 541)	291 (258 - 324)	133 (76 - 190)	1076 (958 - 1194)
2	164 (163 - 165)	35 (32 - 38)	497 (444 - 550)	296 (263 - 329)	133 (76 - 190)	1125 (1007 - 1243)
3	107 (106 - 108)	18 (16 - 20)	539 (484 - 594)	318 (284 - 352)	131 (74 - 188)	1114 (995 - 1233)
4	110 (109 - 111)	25 (23 - 27)	506 (452 - 560)	300 (266 - 334)	132 (75 - 189)	1074 (956 - 1192)
5	151 (150 - 152)	31 (28 - 34)	500 (447 - 553)	297 (264 - 330)	133 (76 - 190)	1111 (993 - 1229)
6	119 (118 - 120)	30 (27 - 33)	493 (440 - 546)	293 (260 - 326)	133 (76 - 190)	1067 (949 - 1185)
7	118 (117 - 119)	18 (16 - 20)	540 (485 - 595)	319 (285 - 353)	131 (74 - 188)	1125 (1006 - 1244)
8	117 (116 - 118)	24 (22 - 26)	507 (453 - 561)	301 (267 - 335)	132 (75 - 189)	1081 (963 - 1199)
9	147 (146 - 148)	31 (28 - 34)	500 (447 - 553)	297 (264 - 330)	133 (76 - 190)	1107 (989 - 1225)
10	147 (146 - 148)	7 (6 - 8)	563 (506 - 620)	331 (296 - 366)	130 (73 - 187)	1178 (1057 - 1299)

(a) Costs of further diagnostic exams to correct wrong diagnoses

3.2.2 Scenario analyses

Table 45Table 44 shows the probabilistic results of the scenario analysis in children. In most scenarios, the rank remains unchanged with a few exceptions. When prevalence was increased, strategies with higher sensitivity but lower specificity, such as strategy 8, becomes more cost effective. In all the other scenarios considered, strategy 1 or 3 consistently retained their position as the most cost-effective options. Strategy 3 became considerably more cost-effective when IgE was used instead of skin prick test, partly due to the cost advantage of using a single blood sampling for both IgE and blood eosinophils.

Table 45: Probabilistic scenario analyses – Children

Scenario	1st ranked	2nd ranked	3rd ranked
Base case	Strategies 1 & 6 (93%)	Strategy 8 (4%)	Strategy 4 (3%)
High prevalence of asthma (80%)	Strategy 8 (41%)	Strategies 4 & 6 (43%)	Strategy 1 (4%)
Low prevalence of asthma (40%)	Strategy 1 (68%)	Strategy 6 (31%)	Strategies 2 and 4 (10%)
IgE instead of skin prick test	Strategy 6 (62%)	Strategy 1 (37%)	Strategy 4 (1%)
Maximum 1 year with a false negative diagnosis	Strategy 1 (60%)	Strategy 6 (38%)	Strategies 4 & 8 (1%)
Maximum 5 years with a false negative diagnosis	Strategy 6 (44%)	Strategy 1 (17%)	Strategy 8 (24%)

Scenario	1st ranked	2nd ranked	3rd ranked
Log-logistic instead of exponential for time-to-first exacerbation	Strategies 1 & 6 (93%)	Strategy 8 (4%)	Strategy 4 (3%)
No QoL reduction in people with untreated asthma	Strategy 1 (75%)	Strategy 6 (25%)	Strategy 2 (0%)
Scotland settings	Strategies 1 & 6 (93%)	Strategy 8 (4%)	Strategy 4 (3%)
GP conduct diagnostic tests	Strategies 1 & 6 (86%)	Strategy 4 (8%)	Strategy8 (5%)
10 minutes required for PEFv	Strategies 1 & 6 (93%)	Strategy 8 (4%)	Strategy 4 (3%)
Low FeNO activity	Strategies 1 & 6 (93%)	Strategy 8 (4%)	Strategy 4 (3%)
High FeNO activity	Strategies 1 & 6 (93%)	Strategy 8 (4%)	Strategy 4 (3%)
FeNO included in all monitoring visits	Strategies 1 & 6 (93%)	Strategy 8 (4%)	Strategy 4 (3%)
ICS + SABA as treatment in adults	Strategies 1 & 6 (93%)	Strategy 8 (4%)	Strategy 4 (3%)
Soluble prednisolone for asthma exacerbation in children	Strategies 1 & 6 (93%)	Strategy 8 (4%)	Strategy 4 (3%)

4 Discussion

4.1 Summary of results

This health economic model was developed to identify the most cost-effective combinations or sequences of tests to diagnose asthma in adults and children with respiratory symptoms. Table 46 illustrates the most cost-effective diagnostic strategy identified in adults and children.

Table 46: Most cost-effective strategies in children and adults

Population	Approach	1st step	2nd step	3rd step	4th step
Adults	**Gradual rule-in**	Blood Eosinophils	+: Diagnose asthma -: BDR	+: Diagnose asthma -: Methacholine	—
Children	**Rule-in-rule-out**	FeNO	+: Diagnose asthma -: SPT/IgE	+: Methacholine -: Exclude asthma	—
		FeNO	+: Diagnose asthma -: SPT/IgE	+: Blood eosinophils -: Exclude asthma	+: Diagnose asthma -: Methacholine

Abbreviations: BDR: bronchodilator reversibility; FeNO: Fractional exhaled nitric oxide; SPT: skin prick test

In adults, the model found that a gradual rule-in approach was cost-effective. The most cost-effective sequence of tests consisted in an initial blood eosinophils test, followed by a re-test with BDR if the initial results were negative and a final re-test with methacholine for those negative on both previous tests.

In children, the model found that a rule-in-rule-out approach was cost-effective. Two similar strategies emerged as the most cost-effective:

1. A three-step strategy involving an initial FeNO, followed by a skin prick test or IgE if FeNO was negative and a final bronchial challenge with methacholine if positive in the second step
2. A long four-step variation including an additional blood eosinophil test to rule in asthma before the final methacholine test

The four-step strategy was found to be particularly useful and cost-effective when IgE is used in the second step, as both IgE and blood eosinophil can be conducted using the same blood sample.

The results were robust in both populations. All the potentially cost-effective strategies in adults reflect a gradual rule-in approach, involving two initial specific tests and a final all-round test. Likewise, all the potentially cost-effective strategies in children reflect the rule-in-rule-out approach, consisting in an initial specific test, a further sensitive test and a final all-round test.

In almost all scenario analyses, the ranks of the strategies remained unchanged in both children and adults, suggesting that there is a high likelihood that the strategies identified were the most cost-effective. FeNO was a cost-effective initial test in adults only when its specificity reaches the value of that of a blood eosinophils test.

4.2 Limitations and interpretation

This analysis had some limitations.

Firstly, diagnostic accuracy of tests in adults was estimated using RADicA study. Despite the alignment of inclusion and exclusion criteria with the clinical review protocol, the sample size was relatively small, with only 118 participants. This could potentially undermine the internal and external validity of the study, although the committee confirmed that the accuracy measured in RADicA met their expectations.

There was some uncertainty regarding the true accuracy of FeNO in the clinical review. A few studies(Kowal, Bodzenta-Lukaszyk, Zukowski, 2009, Schneider, Brunn, Hapfelmeier, Schultz, Kellerer, Jorres, 2022) using the same cut-off value of 50 ppb found a higher specificity (between 0.91 and 0.99) than the estimation derived from RADicA. Furthermore, in the clinical review, the specificity of blood eosinophils was generally estimated to be lower compared to RADicA, with only one study reporting(Nekoee, et al., 2020) a value above 0.9 in adults. Therefore, a threshold analysis on the specificity of FeNO was conducted, which found that FeNO becomes a cost-effective initial test when its specificity approaches that of blood eosinophils.

Not all the participants in RADicA had a recorded measurement in all tests. Specifically, there were several instances of missing values for PEFv, possibly attributable to poor patient compliance. Similar gaps were observed in the context of methacholine and mannitol challenge tests. When calculating the accuracy of a specific strategy, people who reached a particular step but had a missing value for that test, were dropped from the analysis. This may introduce bias if the likelihood of having a missing value is correlated with having or not having asthma because, for instance, people may comply less with PEFv if they do not have asthma symptoms. Therefore, strategies including PEFv, particularly at the first step, should be interpreted with caution. Missing values for methacholine are less problematic as the test was only included at the last step, which is not reached by the entire cohort. Though, this could still introduce biases, particularly if the probability of having a missing value on methacholine is associated with having or non-having asthma. Mannitol test has a significant amount of missing values (50%) as the test was not mandatory and offered to participants only after methacholine, at their discretion. Therefore, bronchial challenge test with mannitol was excluded in any base case analysis scenario. This should not represent a major limitation of the analysis as the committee agreed that methacholine is more frequently used in current clinical practice. Moreover, when mannitol was tested instead of methacholine, no difference was wound in the relative cost-effectiveness of the strategies.

The accuracy of diagnostic tests in children was derived from the clinical review. The quality across the studies included was variable with some exhibiting a very low quality. In particular, the study(Drkulec, Nogalo, Perica, Plavec, Pezer, Turkalj, 2013) used to inform the diagnostic accuracy of IgE and skin prick test was considered of very low quality as the methods of participant selection and information on ICS use prior to study entry were not provided. Likewise, the study(Zaczeniuk, Woicka-Kolejwa, Stelmach, Podlecka, Jerzynska, Stelmach, 2015) used to derive the accuracy of a bronchial challenge test with methacholine in children was deemed of very low quality due to unclear participant selection, interpretation of the index test and reference standard and the flow and timing of patient through the studies. However, no higher-quality studies were available and the committee agreed that these limitations are not expected to significantly undermine the estimation of the diagnostic accuracy.

This analysis used a multivariate probit model to estimate the accuracy of diagnostic tests in children. Probit regression is ideal to model dichotomous outcome, such as the binary results of a test: positive (1) or negative (0). Moreover, the use of multivariate regression allowed to estimate the results of the tests simultaneously, ensuring that the observed correlations in RADicA are maintained. Potential limitations of this methodology might be caused by the

underlying data used to simulate test results. In particular, the correlation matrix had non-statistically significant negative values, which were likely caused by the sample size of the study. To mitigate potential biases, negative values were treated as statistical errors for perfectly independent tests (correlation equal 0). Similarly, correlation between tests could not be estimated for BDR and methacholine challenge tests in people without asthma, as both exhibited perfect specificity. Therefore, correlation values in people without the disease for these two tests was derived from people with the disease. This is not expected to introduce significant biases as the rate agreement between tests results should be similar in those with the disease and those without.

As anticipated, there is no study on the natural history of people with untreated asthma, so a proxy population was used to estimate exacerbation rates and excess mortality: people treated with PRN SABA only. This population exhibited the worst outcomes in the existing literature, as SABA is an effective reliever therapy but not particularly effective in preventing future exacerbations and hospitalisations. However, it is possible that the model is still underestimating negative health outcomes in people with untreated asthma, potentially leading to an underestimation of the cost-effective of strategies with higher sensitivity.

The model allows remission from asthma in the analyses conducted in children. This was agreed by the committee, as in their clinical experience, around 50% of those who are diagnosed with asthma during their childhood, grow out of it. Although there are instances in the real world of people exhibiting remitting-relapsing symptoms of asthma, no quantitative evidence was identified. Therefore, the model assumes that upon achieving remission, people are free of asthma symptoms for the entire duration of their life. Although this could potentially lead to an underestimation of lifetime costs, it is not anticipated to introduce significant biases as time of diagnosis is not expected to influence the likelihood of remission or relapse.

Time dependency was built into the model for exacerbations, mortality and quality of life. However, due to the lack of evidence, the same could not be done for time spent with a false negative diagnosis or time spent waiting for a diagnosis while still in the diagnostic pathway. The first could be problematic if time spent with untreated asthma is correlated with future adverse outcomes occurring after the treatment is started, such as a more difficult to control asthma or higher mortality. If this is the case, it is possible that the model is underestimating the cost-effectiveness of strategies with a higher sensitivity. The latter is considered less concerning, particularly for strategies with only three tests, as waiting time between tests is not expected to be particularly long. However, this may not always apply, particularly for tests such as FeNO, skin prick test or bronchial challenge that are unevenly distributed across the country. In such cases, it is possible that the model is overestimating the cost-effectiveness of strategies with a large use of FeNO, skin prick test or bronchial challenge test with methacholine.

Finally, the model does not distinguish between atopic and non-atopic asthma. Atopic or allergic asthma is more predominantly seen in young people, whereas late onset of the disease is generally associated with non-atopic asthma(Gerday, et al., 2022). Diagnostic tests measuring responsiveness to aeroallergens (skin prick test and IgE) or inflammation (FeNO) are highly accurate in people with atopic asthma but less in those with non-atopic asthma. In children, the model found that the most cost-effective algorithm includes FeNO, skin prick test or IgE and blood eosinophils, all expected to perform poorly in children with non-atopic asthma. Hence, although the algorithm is optimal for the majority of children with atopic asthma, it may fail to detect children with non-atopic asthma. BDR, albeit not as cheap as FeNO, measures lung airway's function, so it can identify children with atopic or non-atopic asthma alike. A strategy beginning with BDR instead of FeNO was found to be the fifth most cost-effective algorithm in children. In adults, the most cost-effective strategy includes BDR for those who tested negative for blood eosinophils. Therefore, the committee agreed

that adults with non-atopic asthma who were misdiagnosed by the blood test would be detected once they undergo BDR testing.

Finally, although time dependency was built into the model for exacerbations, mortality and quality of life, it could not be incorporated for time spent with a wrong diagnosis and time spent in the diagnostic algorithm. The first could be problematic if time spent with untreated asthma is correlated with future adverse outcomes once the treatment is started, such as a higher mortality or increased risk of exacerbations.

4.3 Generalisability to other populations or settings

This analysis is based on people with symptoms suggestive of asthma who have not been initiated to an ICS treatment yet. In reality, many of those who undertake an objective test for asthma are already on an ICS treatment, which could impact the test results. Consequently, the results of this analysis might not be applicable to those who are already on a treatment. Likewise, smoking is a known factor affecting the results of tests, such as FeNO, and so cautioun is advised when applying this strategy to people who smoke.

The current practice for diagnosing asthma in the UK often involves a “trial of treatment” where people with asthma-like symptoms receive an ICS inhaler and the diagnosis is made based on people’s response to the treatment. This was considered highly inefficient by the committee, as the natural “regression to the mean” of asthma-like symptoms implies that most people would improve over time for reasons unrelated to the treatment. Therefore, a trial of treatment strategy would likely result in a large number of false positive diagnoses. A Canadian study from 2008 found that around 30% of people with a diagnosis of asthma did not have the disease(Aaron, Vandemheen, Boulet, McIvor, FitzGerald, Hernandez, Lemiere, Sharma, Field, Alvarez, Dales, Doucette, Fergusson, 2008). Likewise, Shaw and colleagues(Shaw, Green, Berry, Mellor, Hargadon, Shelley, McKenna, Thomas, Pavord, 2012) found that one third of people with a diagnosis of asthma in the UK had normal spirometry and provocation tests. This model found that strategies with low specificity are unlikely to be cost-effective, so a “trial of treatment” strategy with a specificity around 60-70% is very unlikely to be cost-effective.

This analysis is conducted from an English and Scottish perspective so it may not be generalisable to other jurisdictions, particularly if costs of diagnostic tests and asthma management differ across countries. Furthermore, the prevalence of asthma assumed in the model was estimated using an UK study and may not reflect the prevalence in other countries, particularly if there are variations in the criteria for referrals to diagnostic tests.

4.4 Comparisons with published studies

There are two relevant economic studies that look at the most cost-effective sequences or combinations of tests to diagnose asthma. Harnan and colleagues conducted a systematic review and developed an economic model to assess the cost-effectiveness of FeNO either alone or together with other tests(Harnan, et al., 2015). The analysis found that FeNO plus BDR was cost-effective compared to other tests alone, or to FeNO plus spirometry. This aligns well with the results of the adult analysis, which found FeNO and BDR potentially cost-effective tests when included in a “gradual rule-in” strategy. Blood eosinophil was not included in Harnan, so further comparisons are impossible. In children, FeNO was a cost-effective first test only if followed by a highly sensitive test, like skin prick test or IgE. However, like with blood eosinophils, these two tests were not included in Harnan’s.

NICE developed a health economic model in 2017 to assess the most cost-effective sequence of tests to diagnose asthma in adults with respiratory symptoms(National Institute for Health and Care Excellence, 2017). The model found that a strategy involving spirometry, BDR, FeNO, PEFv and methacholine test was cost-effective. This in part aligns with the

findings of this model as the structure identified in the 2017 model resembles a “gradual rule-in” approach. Whereas the 2017 model used committee’s opinion to incorporate correlations between tests, the current model is based on real individual patient data, so correlations are naturally captured. This allowed to estimate a simpler strategy that is not only expected to be cost-effective, but also more easily implementable, considering that the previous algorithm attracted criticism due to its rigidity and high complexity.

4.5 Conclusions

This economic evaluation demonstrated that a “gradual rule-in” approach was the most cost-effective strategy to diagnose asthma in adults. The most cost-effective sequence involved testing all with blood eosinophils, then testing with BDR those who were negative to blood eosinophils and finally reserving methacholine challenge test for those who tested negative to both.

The analysis found that a “rule-in-rule-out” approach was the most cost-effective in children. The most cost-effective sequence involved testing all with FeNO, followed by testing with skin prick test or IgE those who tested negative to FeNO and finally reserving methacholine challenge test for those who were negative to FeNO but positive to skin prick test or IgE.

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