Food Allergy in Children Appendix 3

Health Economics

Appendix 3.0 – Non-IgE-mediated food allergy – Cost effectiveness analysis

Appendix 3.1 – IgE-mediated food allergy – Cost effectiveness analysis

Review of resource use studies for the diagnosis non-IgE-mediated food allergies in children

Sladkevicius E, Nagy E, Lack G et al (2010) Resource implications and budget impact of managing cow milk allergy in the UK. Journal of medical economics 13(1): 119-28		
Guideline topic: Food allergy		Question no:2
Check list completed by Prashanth Kandaswamy		
Section 1: Applicability	**Yes/ Partly/ No/ Unclear/ NA**	**Comments**
1.1 Is the study population appropriate for the guideline?	Yes	Infants with CMA
1.2 Are the interventions appropriate for the guideline?	Yes	
1.3 Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	Yes	
1.4 Are costs measured from the NHS and personal social services (PSS) perspective?	Yes	
1.5 Are all direct health effects on individuals included?	N/A	
1.6 Are both costs and health effects discounted at an annual rate of 3.5%?	No	Not necessary given time horizon
1.7 Is the value of health effects expressed in terms of quality-adjusted life years (QALYs)?	N/A	
1.8 Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	N/A	
1.9 Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?	N/A	
1.10 Overall judgement: Directly applicable/Partially applicable/Not applicable There is no need to use section 2 of the checklist if the study is considered 'not applicable'. Applicable		
Other comments		

Section 2: Study limitations (the level of methodological quality) *This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the clinical guideline*	**Yes/Partly/No/ Unclear/NA Comments**	**Comments**
2.1 Does the model structure adequately reflect the nature of the health condition under evaluation?	Yes	
2.2 Is the time horizon sufficiently long	Yes	A longer time horizon

to reflect all important differences in costs and outcomes?		would be preferable, but current time horizon appears acceptable
2.3 Are all important and relevant health outcomes included?	Partly	
2.4 Are the estimates of baseline health outcomes from the best available source?	Yes	
2.5 Are the estimates of relative treatment effects from the best available source?	Yes	
2.6 Are all important and relevant costs included?	Yes	
2.7 Are the estimates of resource use from the best available source?	Yes	NHS specific costs used
2.8 Are the unit costs of resources from the best available source?	Yes	
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	N/A	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11 Is there no potential conflict of interest?	Partly	Funded by CMA milk maker, but not directly to authors
2.12 **Overall assessment**: Minor limitations/Potentially serious limitations/Very serious limitations Minor Limitations		

Testing for IgE-mediated food allergy – Cost effectiveness analysis

Introduction

The National Institute for Health and Clinical Excellence (NICE) has been asked to produce a guideline on the diagnosis of food allergy in children. This analysis focuses on IgE-mediated food allergy. What follows is the cost effectiveness analysis developed to support the guideline development group (GDG) in coming to recommendations. This analysis has been conducted according to NICE methods outlined in the Guide to the methods of technology appraisals, 2008 and the Guidelines Manual 2009. Therefore, it follows the NICE reference case (the framework NICE requests all cost effectiveness analysis to follow) in the methodology utilised. It is advised that the full guideline should be read as full definitions of terminology will be given there.

Given the paucity of available information GDG opinion was used in the identification and selection of papers and data. In addition, the results presented should be considered exploratory given the significant issues in the quality of data and assumptions made.

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Decision Problem

This guideline is examining two main types of food allergy. Non-IgE-mediated food allergy, examined in appendix 3.0. The other is IgE-mediated food allergy. The decision problem for this type of food allergy is described in Table 1 Decision problem.

Table 1 Decision problem

	Scope	**Approach taken**
Population	Children with suspected IgE-mediated food allergy	Children with suspected peanut allergy
Interventions	Skin prick tests or Serum specific IgE blood test Atopic patch test Double blind placebo-controlled food challenge (DBPCFC)	GP diagnosis plus Skin prick tests or Specific IgE blood test
Comparators	No test	GP diagnosis alone Refer to secondary care
Outcome(s)	Costs, QALYs and Cost per QALY	Cost per QALY

Population

The scope specifies several potential age groups and several food allergies including egg, nut, soya and so on. However, to construct an analysis for each food allergy would be time consuming and also potentially unnecessary. Therefore, only peanut allergies will be considered. This is because it is the most common IgE-mediated food allergy, therefore data should be available. It is also closely associated with the risk of major reactions.

The GDG concluded that only people with a positive clinical history should be tested. Therefore, the populations are those children whose clinical history suggests they have a food allergy. It is likely that it will be possible to extrapolate the results for this population to other allergic diseases.

As will become clearer the majority of children are initially diagnosed at a very young age. Data is available from Ewan et al 1996 which follows children from 1 year to school age (5 years). Therefore, for the model the population will be assumed to be one year old children.

Interventions

The GDG concluded on the basis of the clinical evidence that the only viable tests are the skin prick tests and specific IgE blood tests.

Comparators

The current clinical option is GP diagnosis alone. There is the possibility of referring all children to secondary care however, for implementation reasons this is not possible as the waiting time to see an allergist is already significant. In addition, secondary care diagnosis is beyond the scope of this guideline.

Outcomes

For non-IgE-mediated allergies a cost consequence approach was considered appropriate. However, in this case the expected treatment is an elimination diet. This will not be associated with significant costs and therefore, the benefits to patients of accurate diagnosis need to be accounted for.

Literature reviews

Cost effectiveness studies

No cost effectiveness studies for IgE-mediated food allergy were identified by the literature search therefore a De Novo model will be required.

Treatment pathway

The analysis is examining the value of testing after a GP takes a detailed clinical history. The GDG concluded that testing should be used to confirm a positive diagnosis. If the test is positive treatment should commence, if the test is negative than referral to secondary care is recommended since some other underlying condition may be causing the symptoms. The pathways are summarised in Table 2.

Table 2 Testing pathways - food allergies

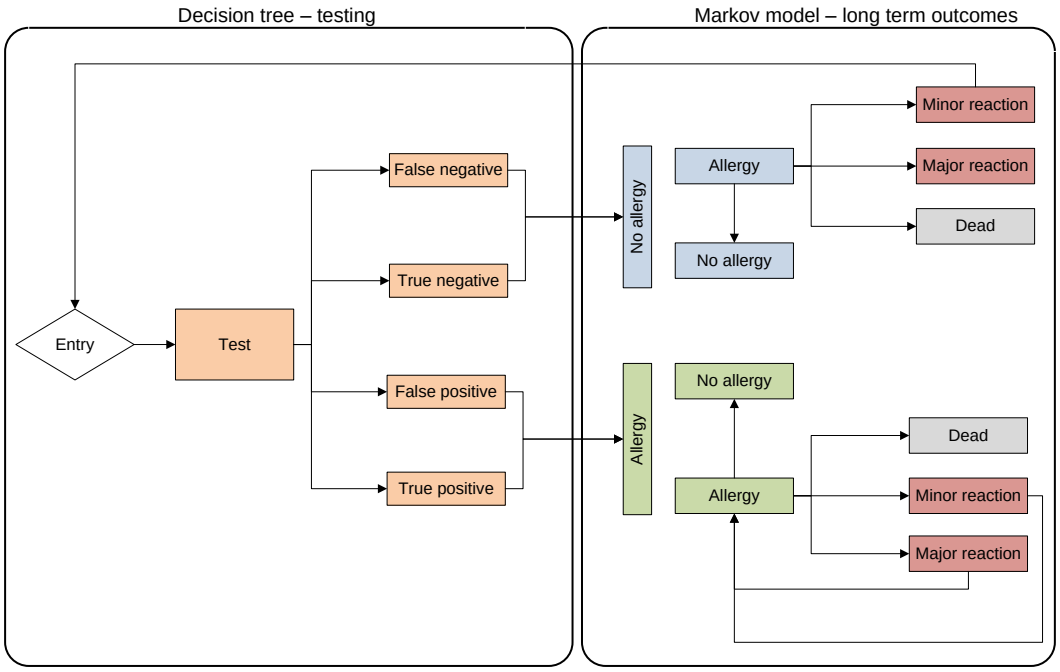
Clinical history	Test	Result
Positive	Positive	Initiate treatment
	Negative	Refer to secondary care
Negative	No test	No action

Therefore, people enter the analysis after a positive clinical history. As a consequence those with a negative history will not be considered.

Model structure

A decision tree will be used to model the diagnosis of food allergy in children and a subsequent Markov model will be constructed to explore the long-term outcomes. The model structure is outlined in Figure 1.

Figure 1 Model structure



The decision tree section of the model is concerned with the proportion of people who are correctly diagnosed with food allergy. People are divided into standard diagnostic categories: True positive, false positive, true negative and false negative. These affect which diagnostic category they are classified as and any potential future management.

The Markov model follows people from their diagnosis. People diagnosed with a food allergy and have an allergy (true positive) will be assumed to stay on an elimination diet and either have a minor, major or fatal allergic reaction. There is also the possibility that they will become desensitised to the allergen and potentially lose their allergy. The false positives will remain in the allergy diagnostic state unless they are retested at a later date.

True negatives remain in the no allergy state and do not move. False negatives are all assumed to have a minor, major or fatal reaction and re-enter the testing schedule.

As this guideline is only examining the diagnosis of food allergy in children rather than the management we will only examine in detail the diagnosis aspect. However, we will explore the impact of various management issues in sensitivity analysis.

Assumptions

- False negatives re-enter testing the next cycle

This assumption is to account for people returning to their GPs if their symptoms have not resolved. It is assumed to happen in the next cycle since the person is not undergoing an active elimination diet. In reality people may take issues into their own hands and initiate elimination diets without the input of a GP or dietician which could have negative effects on the child's health. In addition, they may go straight to secondary care or have the tests done privately. It is not possible to estimate all these potential outcomes therefore, to account for potential NHS resources being used it will be assumed that they re-enter the testing schedule. This will therefore mean that extra resources will be spent on diagnosis.

- False positives have same quality of life as true positives

This is based on the fact that the main impact of allergies on quality of life is from the anxiety of dealing with a major event and also trying to actively avoid events.

- True negatives or false positives do not develop allergies

The majority of allergies develop in the early years of life and therefore, it is unlikely that this is significant factor.

- No age related mortality

For simplicity there will be no other cause mortality. This should not be a major factor given the short time horizon and also the age of the population being tests.

Time horizon

Given the uncertainty over the management of food allergies in this population especially over retesting the base analysis will use a time horizon of 4 years which corresponds with studies that have followed patients with peanut allergies from diagnosis to school age. However, longer time horizons and retesting will be examined in scenario analysis to examine its effect on the cost effectiveness results.

Inputs

Transitions

The following sections outline the key transitions in the model and their source. It was not possible in the time available to conduct a full review. So papers were identified from the literature search that examined natural history and epidemiological studies. The issue here is that the search was not designed to find these studies and therefore, important information may have been excluded. However, for this analysis which is primarily explorative the papers identified should be sufficient. In addition, all values are validated by the GDG.

The proportion of allergies detected by clinical history

Evidence from Sampson and Ho 1997 indicated that in a population of people identified with a clinical history plus a skin prick test and/or a blood test that only 49% were confirmed as having a allergy to peanuts after a food challenge. From experience an estimate of 60% was suggested by the GDG. These figures appear to have validity as a history taking is likely to be very sensitive but not very specific. Given the difficultly in accurately estimating this figure, 49% was used in the base case and then varied in sensitivity analysis.

Sensitivity and specificity of the tests

The estimates for the sensitivity and specificity of the tests were obtained from the clinical review. It should be noted the papers were not of high quality and had several methodological limitations. Therefore, the estimates referred to here should be treated with caution and comparisons between tests should not be undertaken. In addition, this meant that no evidence synthesis could be undertaken such as a meta-analysis. The two methods available would be to use the estimates from the highest quality paper that matches the decision

problem or to use the midpoint from all the studies. For the base case the study which most reflected the population in the decision problem and also using the Youden index as a measure of quality. A sensitivity analysis will be run based on the midpoint from the studies.

Skin prick tests

Based on the evidence review the sensitivity of skin prick test varied from 80 to 100% and for specificity the values varied from 29 to 72%. The highest quality paper was Rance et al 2002. This paper included testing for peanut allergies and all were confirmed with a DBPCFC. It also had the highest Youden score for the tests look at peanut allergies. The base case estimates are summarized in Table 3 along with the midpoints that will be examined in sensitivity analysis.

Table 3 Skin prick test - test accuracy

	Base value	Midpoint	Lower value	Upper value
Sensitivity	100%	90%	80%	100%
Specificity	66.1%	50.5%	29%	72%

IgE Blood tests

Based on the evidence review the sensitivity of IgE blood tests varied from 25 to 97% and for specificity the values varied from 38 to 100%. The highest quality paper was Rance et al 2002. The base case estimates are summarized in Table 4 along with the midpoints that will be examined in sensitivity analysis.

Table 4 IgE blood test - test accuracy

	Base value	Midpoint	Lower value	Upper value
Sensitivity	96.6%	61%	25%	97%
Specificity	62.4%	69%	38%	100%

Secondary care – double blind food challenge

The double blind food challenge is often considered the gold standard test for food allergies in children and as such is associated with near 100% sensitivity and specificity. The GDG noted that often secondary care did not always achieve this due to pressure on resources. Therefore, the base case will assume a 98% sensitivity and specificity. These values will be varied in sensitivity analysis.

Probability of minor reaction

Fajt and Green 2008 suggested that 75% of patients with a known peanut allergy experience a reaction caused by inadvertent exposure. With an annual incidence estimated at around 14%. In the model the value of 14% is used.

Probability of major reaction

Hourihane 2006 reported that 229 children were admitted to hospital between 1998 and 2001. According to Gupta et al 2004 11.8 per 100,000 0-14 year olds were admitted to hospital for allergies. This gives a probability of 0.000118.

Probability of fatal reaction

Hourihane 2006 in a review article on the dangers of food allergy estimated that 1 death in every 830,000 is due to food allergies each year. This gives a probability of 0.0000012.

Desensitisation of allergies

The estimate for the proportion whose allergy regresses was obtained from Ewan et al 1996. This paper was identified by daisy chaining from the natural history papers which all referred to this paper. Ewan et al 1996 followed a series of children with nut allergies from diagnosis (average age 1 year old) till school age (5 years old). At the end of the study 20% of the children had become desensitised to nuts. This figure of 20% is confirmed by Hourihane et al 1998 and Skolnick et al 2001. To convert these into three monthly transitions to fit the cycle length the following formula will be used where p is the yearly probability (Briggs et al 2003):

$$3\ monthly\ probability = 1 - e^{((\ln 1-P)*(1/4))}$$

The final transition matrix is presented in Table 5

Table 5 Final transition matrix for long term outcomes up to 5 years of age

	Allergy	No Allergy	Confirmed Allergy	Confirmed No Allergy	Minor	Major	Dead
Allergy	0	0.01385	0	0	0.986	0.00003	0.0000012
No Allergy	0	1	0	0	0	0	0
Confirmed Allergy	0	0.01385	0.949	0	0.037	0.00003	0.0000003
Confirmed	0	0	0	1	0	0	0

No Allergy							
Minor	0	0	1	0	0	0	0
Major	0	0	1	0	0	0	0
Dead	0	0	0	0	0	0	1

Quality of life review

Literature

A search for quality of life papers identified 38 papers. The papers can be split into 4 groups. 11 papers were concerned with the development of quality of life measures for people with food allergies. These shall not be considered here. The other 3 groups include 16 papers which review the quality of life of children with food allergies including qualitative studies and narratives. 5 papers examined the affect of food allergies on children and their parents/carers. Only three papers collected quality of life information in people with food allergies with instruments appropriate for the calculation of QALYs (that is an instrument on a 0 to 1 scale with 0 equaling dead and 1 perfect health). Given resource constraints we shall review the papers that collected data suitable for the calculation of QALYs and the papers examining the link between children and their parents/carers.

Utilities

The three studies identified all used the Health utility index (HUI) 3 for estimating quality of life. This instrument is explicitly mentioned in the NICE methods guide as appropriate for calculating quality of life.

One study however, Mo et al 2004, used the HUI 3 to calculate the odd ratios to determine what factors were linked to quality of life. It unfortunately did not report the absolute figures and as such was not appropriate for the calculation of QALYs. The remaining two studies are summarised in Table 6.

Table 6 Quality of life papers that collected data suitable for QALYs

Study	Country	Population	Age groups considered?	Baseline	Allergy
Mittmann et al 1999	Canada	Cross sectional survey of people aged 12 to	12-19 20-29 30-39 40-49 50-59	0.94 (0.074) 0.94 (0.069) 0.94 (0.08) 0.93 (0.08) 0.92 (0.07)	0.90 (0.13) 0.91 (0.12) 0.89 (0.14) 0.84 (0.19) 0.83 (0.17)

		80+ n = 17624 collected 1994	60-69 70-79 80+	0.91 (0.079) 0.91 (0.1) 0.88 (0.1)	0.78 (0.18) 0.78 (0.18) 0.64 (0.23)
Mittmann et al 2001	Canada	Cross sectional study of population n = 47534 collected 1996	No specific age group considered	0.953	0.951

Both the Mittmann papers were based on the National population health survey, a prospective national survey of community living Canadians. As can be seen only the Mittmann et al 1999 paper includes stratification by age. The main issues with these papers include the fact that it is a cross sectional survey of a Canadian population and therefore, may not be representative of the UK population. In addition, the 1999 paper is based on the preliminary weights developed for the HUI 3 and therefore, may now be considered inaccurate. Finally while the papers provide some data on the population of interest, it excludes the majority of the population (0 to 12) of interest.

It should be noted that collecting data in very young children is very difficult due to ethical and methodological difficulties. Therefore, the values from Mittmann et al 1999 will be used in the base case and alternative values will be examined in sensitivity analysis.

The quality of life of parents/carers

An overview of the included studies is provided in Table 7.

Table 7 Quality of life papers that examined link between parents/carers and child food allergy

Studies	Type	Population	Quality of life scales?
King et al 2009	Cross sectional questionnaire study	46 families with one child aged 8-12 with an allergy and one older sibling.	World health Organisation Quality of life scale, and a stress and anxiety scale.
Marklund et al 2006	Postal survey	Parents of 134 school children (8-19) (represents a 74% response rate)	CHQ-PF28 and study specific questionnaire
Gupta et al 2008	Focus groups	Parents with children with an allergy (3 groups), physicians (3 groups) and general public (2 groups)	Interviews
Bollinger et al 2006	Questionnaires given to families attending a	87 families with a child between 0 and 18and spoke English	Food allergy Impact scale (study specific questionnaire)

	university based allergy clinic		
Kilgallen and Gibney et al 1996	Interview assisted questionnaire in maternity hospital	Parents of 600 children between 0 to 48 months.	Not specifically collected.

Kilgallen and Gibney et al 1996 specifically examined the perception of food allergy by parents and children rather than quality of life.

None of these papers included data appropriate to calculate QALYs. They were reviewed to see if any of the papers provided an indication of the magnitude difference between the affect of allergies on children and adults. All the papers concluded that the parent's quality of life is adversely affected by a child with an allergy. However, none concluded on the absolute magnitude of the decrement. Therefore, the affect of this additional effect will be explored in sensitivity analysis.

Minor reactions

No suitable values were identified for minor reactions however; it is likely that the quality of life associated with allergies takes this into account as almost 75% of people with a peanut allergy have some form of reaction. Therefore, the utility associated with allergy will be extrapolated to minor reactions.

Major reactions

For major reactions it is very difficult to collect a utility for this event given its severity and potential impact on the patient. Therefore, other NICE guidance was searched for utility estimates. Omalizumab for uncontrolled asthma in children (appraisal ongoing) reports a value of 0.326 for exacerbations requiring hospitalisation. An asthma exacerbation often requires a long hospital stay and the GDG commented that this was also true for major allergic reactions to foods. The GDG considered that it was appropriate to extrapolate this value to this condition.

Costs

The only appropriate costing paper identified by the search was Sladkevicius et al 2010 which specifically examined cow's milk allergy, a mainly non-IgE-mediated food allergy. Sladkevicius et al 2010 obtained all the costs from

public sources such as the NHS reference costs and the PSSRU. Therefore, these references will be used to identify the key costs in the analysis.

The key costs that will be considered are described in the following sections.

Diagnostic

GP history taking

All GP appointments are meant to take 10-15 minutes and therefore according to the PSSRU the cost of a GP appointment is £180.

This cost is applied to all diagnostic strategies to represent the initial history taking; this is used particularly when taking into account retesting.

Skin prick tests

There is no appropriate NHS reference cost for skin prick testing and therefore a micro costing approach was taken. Communication with manufacturers and GDG members produced a list of components and prices which are summarised in Table 8.

Table 8 Cost breakdown for skin prick tests

Component	Base case	Lower limit	Upper limit	Source	Distribution
Cost of vials	£17	12	£34	GDG	Uniform
No of drops per vial	80	60	100	GDG	Uniform
Lancet (200)	12	6	18	GDG	Uniform
Controls x2	12	6	18	GDG	Uniform
Nurse time minutes	30	20	90	GDG	Uniform
Nurse cost per minute	0.483	0.242	0.725	PSSRU 2009	Uniform
GP time minutes	10	5	45	GDG	Uniform
GP cost per minute	3	1.5	4.5	PSSRU 2009	Uniform
No of allergies tested for	8	5	16	GDG	Uniform

For GPs to run a service in their practices they would need to train a nurse to carry out the procedure and to buy the items in bulk. Therefore, setup costs could be considered. However, the way these should be considered is not clear. The usual way to model setup costs is to annualize them and then include them in the costing. It would then be possible to estimate the number

of people required to make the test cost effective. However, in this case there are no capital costs, only consumerables. Therefore, the numbers tested each year should be considered. To do this in a traditional Markov model is not simple unless we include a dynamic population. This level of complexity is not possible in the current analysis and therefore, will not be considered explicitly.

IgE blood tests

Similarly for the Skin prick tests there was no publically available reference cost for carrying out IgE blood tests in primary care. Therefore, again a mixture of communication with pathology labs and GDG members were used to generate the estimates. The values chosen are summarised in Table 9.

Table 9 IgE blood tests cost breakdown

Component	Base case	Lower limit	Upper limit	Source	Distribution
Cost per allergy tested for	12	6	18	GDG	Uniform
No of allergies tested for	8	5	16	GDG	Uniform
GP time minutes	10	5	45	PSSRU 2009	Uniform
GP cost per minute	3	1.5	4.5	PSSRU 2009	Uniform
Nurse time minutes	2	1	10	GDG	Uniform
HCP cost per minute	0.483	0.242	0.725	PSSRU 2009	Uniform

Secondary care diagnosis

The diagnostic test carried out in secondary care is also assumed to be a double blind oral food challenge. According to information from Manchester hospitals two appointments will be required the first to put someone on a food elimination diet the second to actually carry out the oral food challenge. This could take the form of two outpatient appointments. The suitable code appears to be a consultant led appointment for paediatric clinical immunology and allergy (service code 255) with the corresponding cost of £576 (£288 for each appointment).

Markov model

Confirmed Allergy (including true and false positives)

For the base case it will be assumed that there apart from a food elimination diet that there are no further costs involved. However, epinephrine-pens are often prescribed as part of management to treat potential anaphylaxis. However, their value is questioned and potentially may be overprescribed given the perceived risk of peanut allergies. So as a sensitivity analysis it will be assumed that each child gets prescribed 4 epinephrine-pens two for home and two for school with an average shelf life of six months. It shall also be assumed 36% of children get epinephrine-pens (Watura 2002). The cost of epinephrine-pens from the British National Formulary number 59 is £28. This produces a yearly cost of £76.16.

Confirmed No allergy (including true and false negatives)

No costs will be assumed for the 'no allergy' diagnostic states.

Minor reaction

It is assumed that minor reactions are associated with no costs impact, but a sensitivity analysis will be carried out where people go to their GP for any treatment advice. Ergo a 10 to 15 minute GP appointment will be examined.

Major reaction

It is assumed that a major reaction is one that requires hospitalisation. It will be assumed to be a inpatient visit since it may require an overnight stay. The appropriate NHS reference cost is likely to be Shock and anaphylaxis without CC (WA16Y) with a corresponding cost of £991.

Analyses

Given the quality of the evidence available and the considerable uncertainties involved, significant sensitivity analyses will be required.

Deterministic sensitivity analysis

All variables in the model will be varied by finding using the upper and lower values, where these were not available 50% increase/decreases will be used.

The time horizon will also be explored by extending it to the age of 18. Data on the desensitization of allergies after five years is not available and therefore, it will be assumed that after five years no one becomes desensitized to allergies.

The cost of treatment will be explored via the addition of epinephrine-pens and also minor reactions being associated with a GP visit.

Scenario analysis

Retesting

Children often grow out of their allergies as they get older and as such will get reviewed regularly. This may involve retesting. Therefore, retesting every year until school age will be explored to see what effect it has on the cost effectiveness results. Re-testing will only look at those previously diagnosed as having an allergy to examine whether they have outgrown it and become desensitized to the allergy. In addition, it will be assumed that the children are being retested with the same diagnostic tool they were diagnosed with originally.

Parent's quality of life

As mentioned in the quality of life section there is evidence of a link between a child's food allergy and their parent/carer and even their siblings. However, no evidence was identified to suggest what the magnitude of this effect is. Therefore, the magnitude will be explored in sensitivity analysis. This will be done by multiplying the QALY gain by a factor to account for any parental gain.

Probabilistic sensitivity analysis

Table 10 outlines the variables that are included in the sensitivity analysis along with distributions:

Table 10 Variables included in probabilistic sensitivity analysis

Variable		Mean	Distribution	Standard error	A	B
Skin prick test sensitivity		1	Uniform	[redacted]	0.8	1
Skin prick test specificity		0.661	Uniform		0.29	1
IgE blood test sensitivity		0.966	Uniform		0.25	1
IgE blood test specificity		0.624	Uniform		0.38	1
Secondary diagnosis sensitivity		0.98	Uniform		0.85	1
Secondary diagnosis specificity		0.98	Uniform		0.85	1
Allergy to no allergy		0.054258	Beta	100*	5.43	94.57
Allergy to minor		0.14	Beta	100*	14	86
Allergy to major		0.000118	Beta	100000*	11.8	99988
Allergy to dead		0.0000012	Beta	830000*	0.996	829999
Confirmed allergy to no allergy		0.054258	Beta	100*	5.43	94.57
Confirmed allergy to minor		0.14	Beta	100*	14	86
Confirmed allergy to major		0.000118	Beta	100000*	11.8	99988.2
Confirmed allergy to dead		0.0000012	Beta	830000*	0.996	829999
Quality of life						
No allergy		0.235	Beta			
Allergy		0.225	Beta			
Minor		0.235	Beta			
Major		0.0815	Beta	0.05	2.359	26.584
Cost						
Secondary diagnosis cost		516	Gamma	386.86	1.779	290.042
Major reaction		991	Gamma	188.16	27.739	35.726
GP history taking	GP appointment time * GP cost per minute = Total					
	GP appointment time	15	Uniform	[redacted]	5	15
	GP cost per minute	3	Uniform		1.5	4.5
Skin prick test	Total	(((a/b)+(c/200))*i)+(d/b)+(e*f)+(g*h)				
	Cost of vials (a)	17	Uniform		12	34
	No. of drops per vial (b)	80	Uniform		60	100
	Lancet (200) (c)	12	Uniform		6	18
	Controls x2 (d)	12	Uniform		6	18
	Nurse time minutes (e)	30	Uniform		20	90
	HCP cost per minute (f)	0.483	Uniform		0.242	0.725
	GP time minutes (g)	10	Uniform		5	45
	GP cost per minute (h)	3	Uniform		1.5	4.5
	No of allergies tested for (i)	8	Uniform		5	16
IgE blood test	Total	(u*v)+(v*x)+(y*z)				
	Cost per allergy tested for (u)	12	Uniform		6	18
	No of allergies tested for (v)	8	Uniform		5	16
	GP time minutes (w)	10	Uniform		5	45
	GP cost per minute (x)	3	Uniform		1.5	4.5
	Nurse time minutes (y)	2	Uniform		1	10

	HCP cost per minute (z)	0.483	Uniform	[redacted]	0.242	0.725
Cost of managing allergies	Total	I*II*III				
	Proportion receiving epinephrine-pens (I)	0.34	Uniform	[redacted]	0	1
	Number of epinephrine-pens (II)	4	Uniform		1	6
	Cost of epinephrine-pens (III)	28	Uniform		20	35
*is the sample size this is then used to calculate A and B, where A is the mean and B is sample size – mean.						

The reason for the number of uniform distributions was an absence of information informing the estimates. Therefore, a uniform distribution accurately represents the current knowledge about the values.

Quality of life values

A novel approach will be used for the probabilistic sensitivity analysis for utilities. Since the utilities for the health states decrease with the severity of the condition it will be necessary to ensure that in any probabilistic sensitivity analysis this remains true otherwise counterintuitive results will be produced. Therefore, beta distributions of the differences between the estimates will be used to ensure that the probabilistic results remain consistent. Table 11 outlines the utilities that are varied according to their difference. The standard error of the difference was calculated using the following formula:

$$SE(of\ difference) = \sqrt{(\left(\frac{sd^2}{n_a}\right) + \left(\frac{sd^2}{n_b}\right))}$$

Where sd = the standard deviation of the source population, n = the size of the sample.

Table 11Quality of life estimates in probabilistic sensitivity analysis

State	Mean	Standard deviation	Difference	Standard error of the difference	Distribution	Alpha	Beta
No allergy	0.94	0.074	NA	NA	Beta	8.742	0.558
Allergy	0.90	0.13	0.04	0.077	Beta	0.251	5.646

Value of information analysis

Value of information analysis is used to identify the parameters which contribute most to decision uncertainty. Decision uncertainty can be defined as the probability that a wrong decision concerning optimal therapy is made

and the consequences of such a wrong decision. Value of information analysis is conducted for all parameters within the model and for different subsets of parameters. Decision uncertainty can be measured in terms of opportunity loss – the probability that a wrong decision is made multiplied by the consequence of these wrong decisions. Value of information analysis can identify the reduction in opportunity loss associated with having perfect information about a parameter or group of parameters. By having perfect information we necessarily will have less uncertainty and thus less opportunity loss.

Expected value of perfect information (EVPI) is the estimate of opportunity loss for all parameters. Expected value of perfect parameter information (EVPPI) is the opportunity loss associated with imperfect information on specific parameters. EVPI and EVPPI will be conducted to identify whether further research is required and in what areas. For EVPI the approximate size of the population is required. Information from Peanut UK indicates that 1.8% of children of school entry age have a peanut allergy. If it is assumed that school entry age is 4 years according to population statistics from the office of national statistics suggests that in 2009 there were 638.8 thousand children of 4 years in England and Wales. Therefore, the potential number of children who could benefit from improved testing is 11,498 children. This value will be used to calculate the population EVPI.

Results

Base case

Deterministic and probabilistic

Table 12 summarises the deterministic and probabilistic results from the economic model all compared to GP diagnosis without a test with a time horizon of 4 years and with the best quality studies used for estimates of sensitivity and specificity:

Table 12 Deterministic and probabilistic cost effectiveness results (per person)

	QALY	Cost (£)	Incremental QALYs	Incremental Costs (£)	ICER (£)
Deterministic					
GP only	3.38	45	0.00	0.00	£0.00
IgE blood test	3.59	464	0.21	419	£1,990
Skin Prick Test	3.60	414	0.22	369	£1,657
Probabilistic					
GP only	3.36	45	0.00	0	0.00
IgE blood test	3.47	579	0.11	534	£4,824
Skin Prick Test	3.47	559	0.11	514	£4,563

These results indicate that the tests are cost effective compared to not using a test and that overall skin prick testing is more cost effective than IgE blood testing. The difference between the deterministic and probabilistic sensitivity analysis is due to the number of uniform distributions. This particularly evident since the majority of uniform distributions are allocated to costs and the incremental cost appears to be the variable that is significantly different between the deterministic and probabilistic.

Sensitivity analysis

One-to-one sensitivity analysis

Figure 2 and Figure 3 display the tornado graphs from the deterministic sensitivity analysis for IgE blood and skin prick tests.

Figure 2 Deterministic sensitivity analysis - IgE blood tests

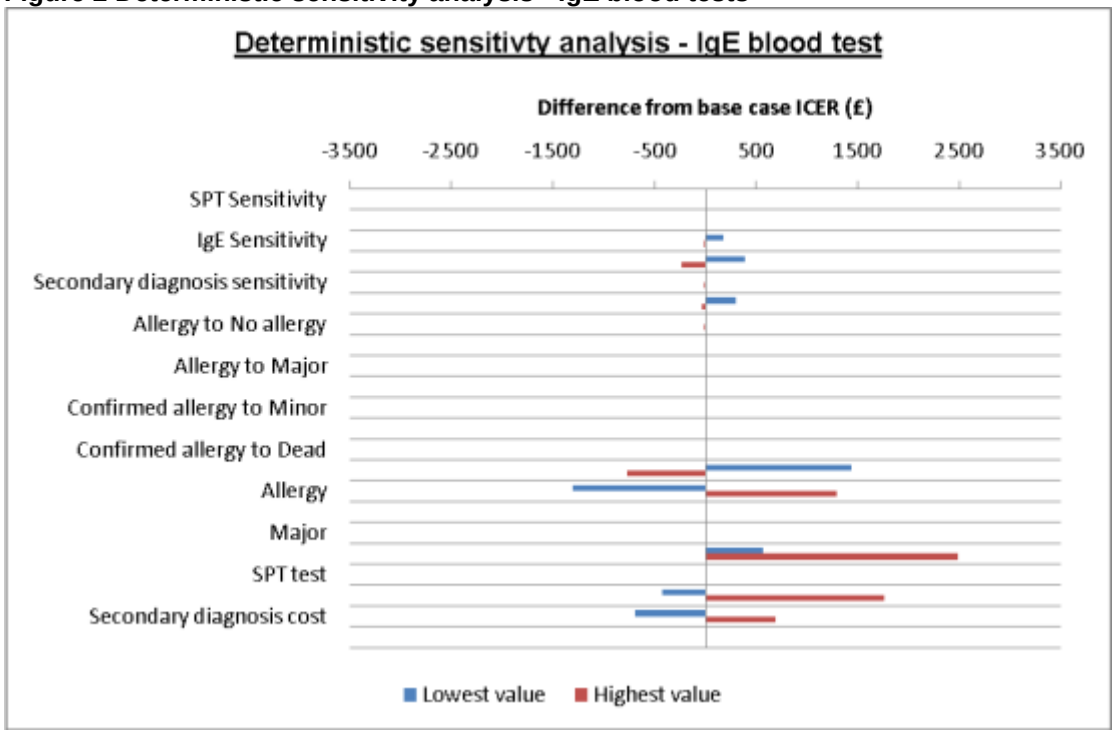
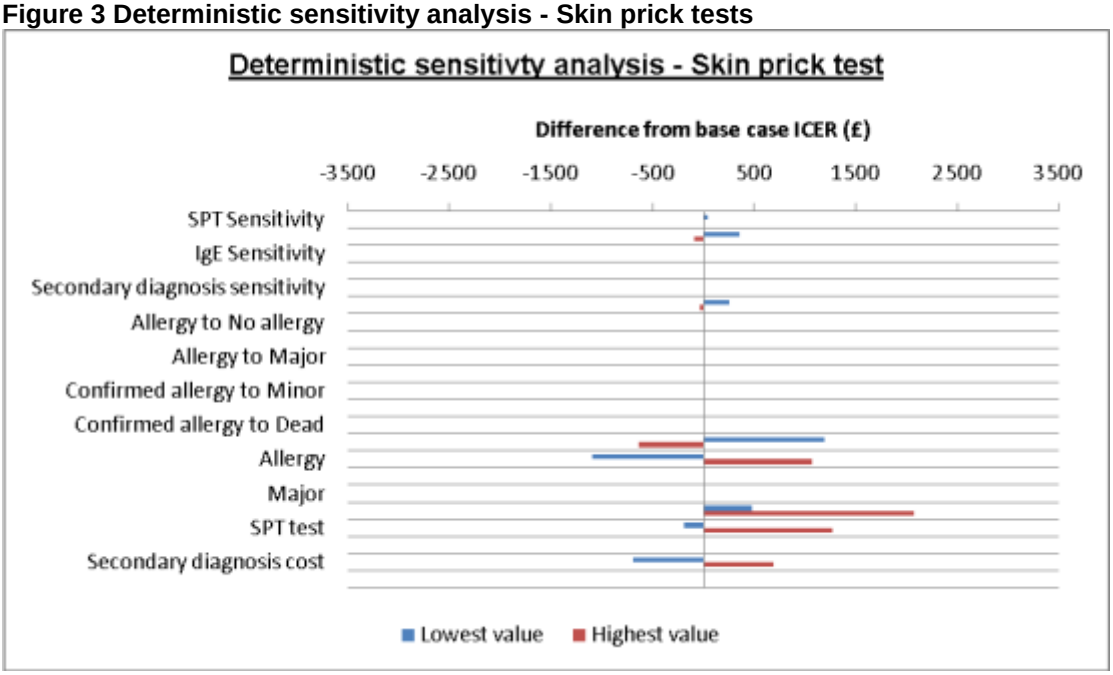


Figure 3 Deterministic sensitivity analysis - Skin prick tests



These results indicate that none of the analyses result in the ICERs going over £20,000 per QALY. The biggest drivers are the quality of life difference between having an allergy to no allergy and the cost of the tests. As can be see the long term outcomes do not significantly affect the ICER. This is probably due to the small percentages involved.

Time horizon

Table 13 presents the ICERs for both tests at different time horizons. These probably represent overestimates since it is assumed that children cannot move diagnostic categories unless they are retested. In reality it is likely that children will discover by accident they no longer have an allergy. So the quality of life loss would be lower ergo the ICERs would be higher.

Table 13 Cost effectiveness of tests at different time horizons

	Time horizon (Age)						
Test	**1**	**2**	**3**	**4**	**5**	**10**	**18**
IgE blood test	£20,008	£7,723	£4214	£2,685	£1873	£585	£214
Skin Prick Test	£14,167	£5,484	£2995	£1,909	£1331	£416	£152

Retesting

Table 14 presents the results of the inclusion of yearly retesting.

Table 14 Cost effectiveness results of including yearly testing

	QALY	Cost (£)	Incremental QALYs	Incremental Costs (£)	ICER (£)
Deterministic					
GP only	3.38	210	0	0	0
IgE blood test	3.69	503	0.31	293	£939
Skin Prick Test	3.70	450	0.32	240	£757
Probabilistic					
GP only	3.39	207	0	0	0
IgE blood test	3.56	671	0.17	464.13	£2,752
Skin Prick Test	3.56	649	0.17	441.96	£2,600

The probability that the skin prick test is cost effective at £20,000 per QALY gained is 98% and for IgE blood tests the probability is 94%. These results indicate that the inclusion of future retesting improves the cost effectiveness probably due to the costs of management increasing. Therefore, the value on an accurate diagnosis becomes more valuable.

Cost of managing an allergy

To explore the effect of the prescription of epinephrine-pens it was assumed that people will be allocated 4 pens each with each one costing £28 (BNF). These values were varied between plus and minus 50%. It was assumed that the shelf life is approximately 6 months. Table 15 demonstrates the deterministic and probabilistic results of including these costs.

Table 15 Cost effectiveness results including allergy management

	QALY	Cost (£)	Incremental QALYs	Incremental Costs (£)	ICER (£)
Deterministic					
GP only	3.38	196	0	0	0
IgE blood test	3.59	531	0.21	335	£1,594
Skin Prick Test	3.60	477	0.22	281	£1,262
Probabilistic					
GP only	3.37	177	0	0	0
IgE blood test	3.49	668	0.12	490	£4,084
Skin Prick Test	3.49	650	0.12	472	£3,968

The inclusion of these management costs results in the ICERs decreasing. Skin prick tests are have a 99% probability of being cost effective at £20,000

per QALY gained. For IgE blood tests this probability is 96%. These results indicate that the more expensive management becomes the more cost effective accurate diagnosing becomes.

GP clinical history taking

Table 16 demonstrates the effect of the accuracy of the initial GP history taking on the ICER.

Table 16 GP history taking accuracy and cost effectiveness results

GP clinical history	IgE blood tests	Skin prick tests
1	-£1,008,068	No QALY difference
0.9	£7,528	£3,895
0.8	£4,405	£2,636
0.7	£3,368	£2,217
0.6	£2,851	£2,007
0.5	£2,541	£1,881
0.4	£2,334	£1,797
0.3	£2,186	£1,737
0.2	£2,076	£1,692
0.1	£1,990	£1,657

As the GP clinical effectiveness improves the ICER increases, however, it is only when the value gets over 0.9. This suggests that there is always value in carrying out the test.

Minor reaction cost

Table 17 presents the cost effectiveness results with the addition of an additional GP consultation to those affected by a minor reaction.

Table 17 Minor reaction cost

	QALY	**Cost (£)**	**Incremental QALYs**	**Incremental Costs (£)**	**ICER (£)**
Deterministic					
GP only	3.38	46	0	0	0
IgE blood test	3.59	465	0.21	419	£1,990
Skin Prick Test	3.60	416	0.22	369	£1,657
Probabilistic					
GP only	3.36	63	0	0	0
IgE blood test	3.48	601	0.12	537	£4,455
Skin Prick Test	3.48	575	0.12	512	£4,230

The addition of a cost for minor reactions is that the deterministic results stay the same and the probabilistic results improve. This is because the impact of incorrect diagnosis is now greater and therefore, the cost effectiveness is likely to be less uncertain.

Parent's quality of life

Table 18 demonstrates the effect of including a weight for the parent's quality of life on the ICER.

Table 18 Inclusion of parent's quality of life

Parents weight	IgE blood test	Skin prick test
0	£1,990	£1,657
0.1	£1,809	£1,507
0.2	£1,658	£1,381
0.3	£1,530	£1,275
0.4	£1,421	£1,184
0.5	£1,326	£1,105
0.6	£1,243	£1,036
0.7	£1,170	£975
0.8	£1,105	£921
0.9	£1,047	£872
1	£995	£829

As should be expected as the effect on the parent's quality of life increases the ICER decreases. Therefore, when considering the cost effectiveness estimates the addition of parents quality of life would improve the cost effectiveness of the tests.

Cost effectiveness acceptability curves

Figure 4 cost effectiveness acceptability curvespresents the cost effectiveness acceptability curves (CEACs) which demonstrate the probability of the intervention being cost effective at different thresholds of cost effectiveness.

Figure 4 cost effectiveness acceptability curves

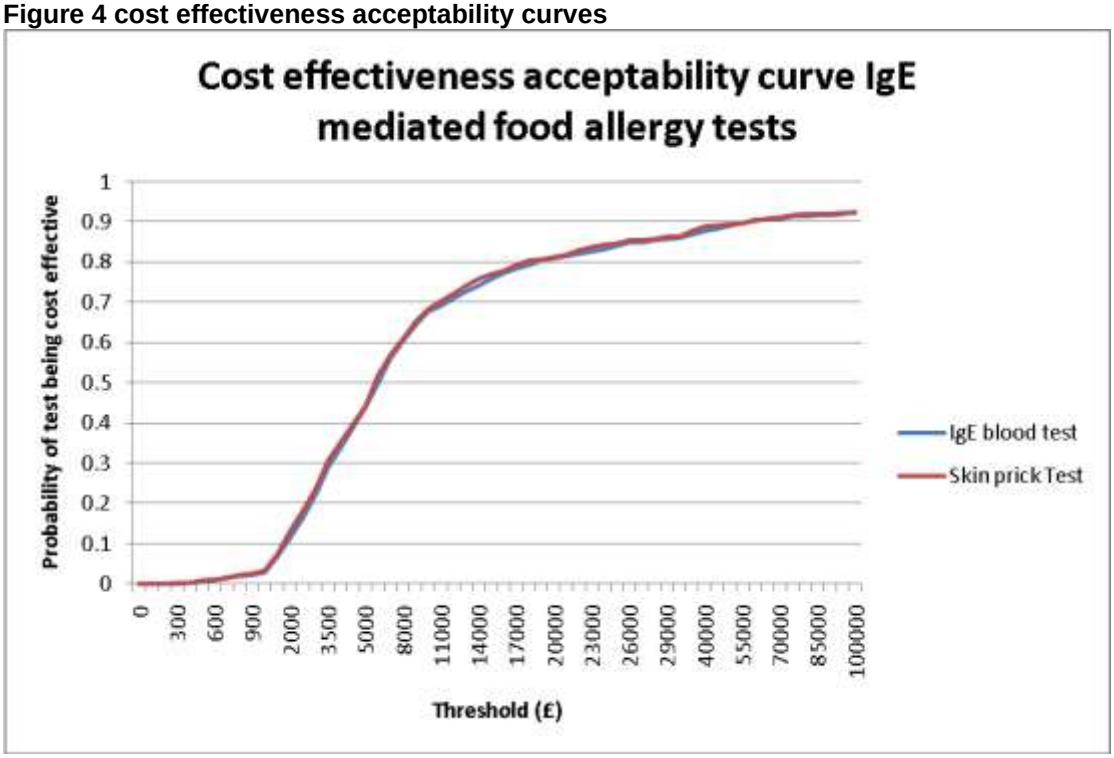


Table 19 gives the probabilities at each threshold.

Table 19 Probability of tests being cost effective at £20,000 and £30,000 per QALY gained

Threshold	IgE blood test	Skin prick test
£20,000 per QALY	81%	81%
£30,000 per QALY	86%	86%

These results indicate that the tests have very high probability of being cost effective with probabilities over 85%. These results though are likely to be highly influenced by the simplified structure of the model.

Cost effectiveness acceptability frontiers

Figure 5 and Table 20 outlines the cost effectiveness acceptability frontier which indicates which option no test, IgE blood test and skin prick test is associated with the greatest gain.

Figure 5 Cost effectiveness acceptability frontier

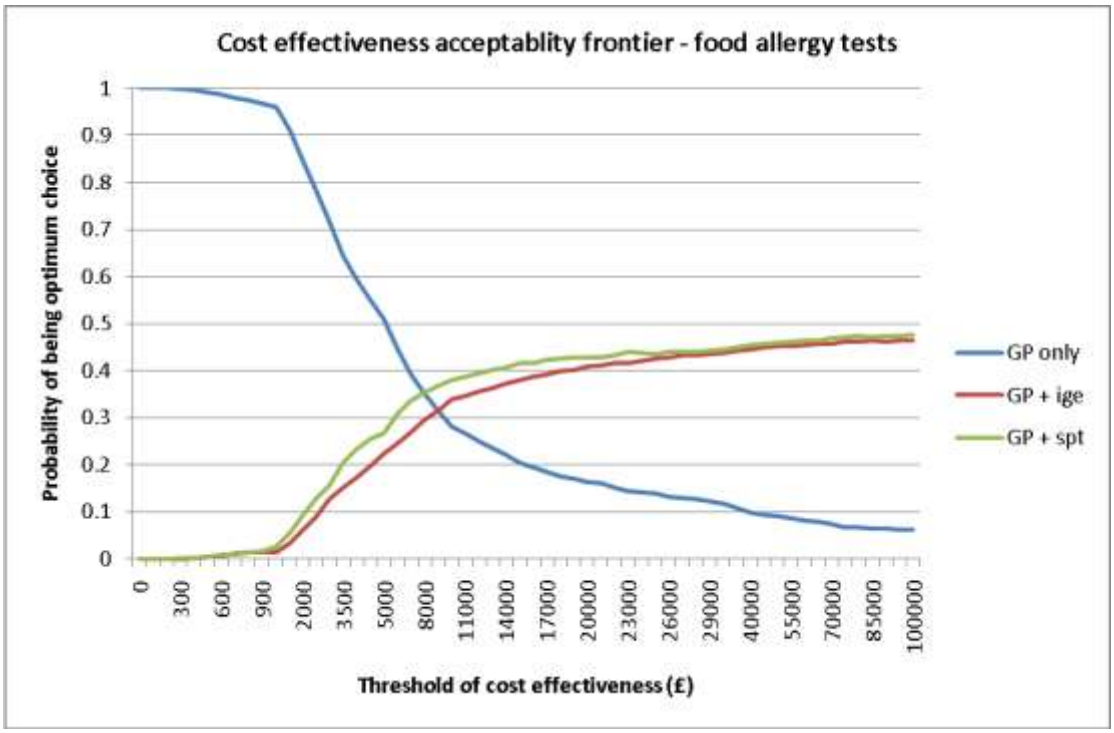


Table 20 Probability of being optimum choice at £20,000 and £30,000 per QALY gained

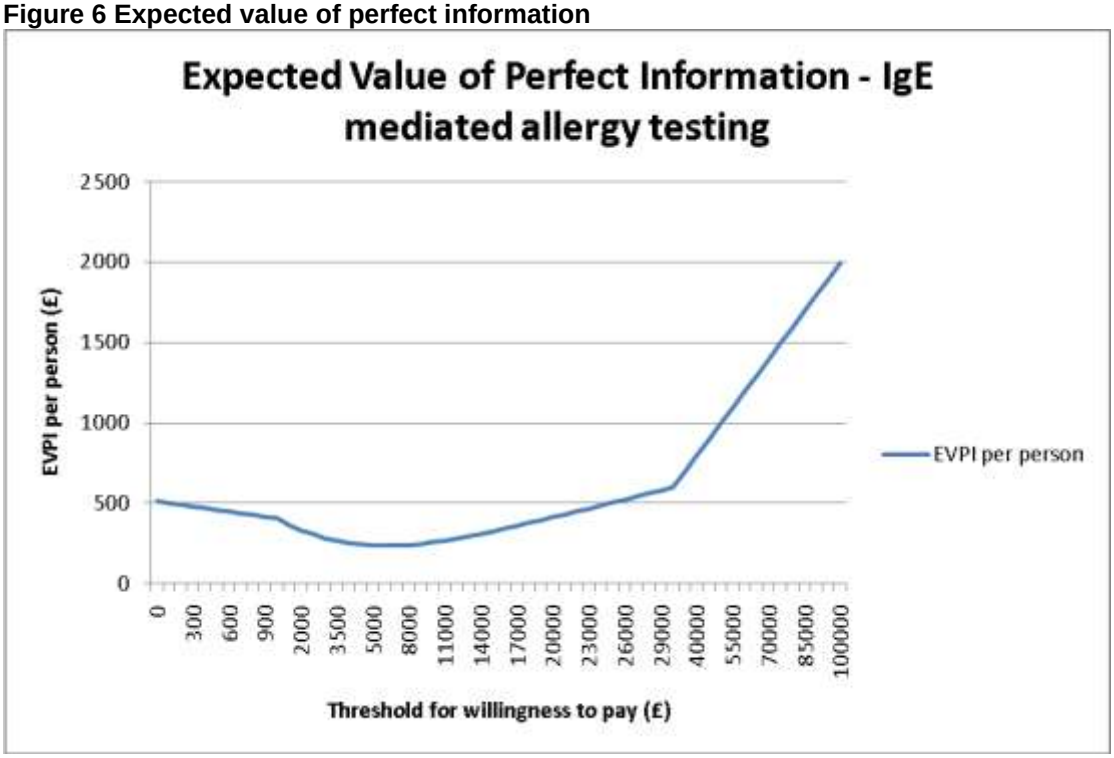
Threshold	GP alone	IgE blood test	Skin prick test
£20,000 per QALY	0.164	0.409	0.427
£30,000 per QALY	0.117	0.438	0.445

These results indicate that of the options skin prick test is likely to be the optimum choice. However, there is little difference between the skin prick test and IgE blood test. These results are going to depend on the number of patients tested per year due to the skin prick test being associated with significant bulk buying.

Value of information

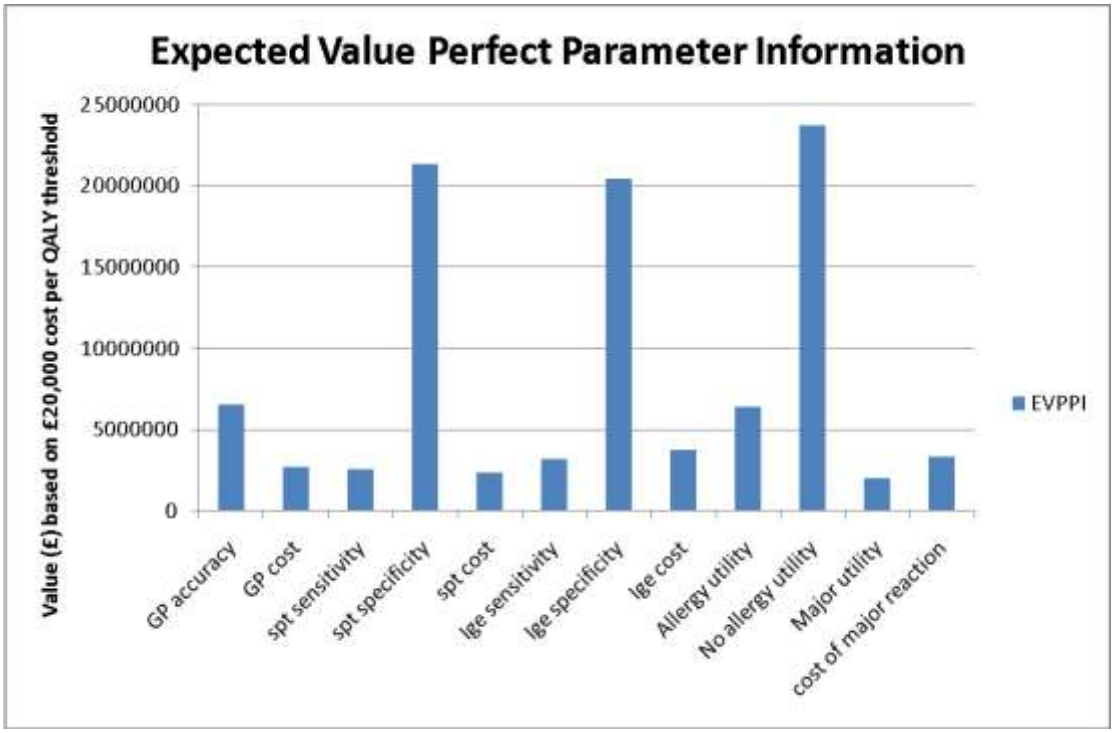
The expected value of perfect information analysis is presented below in Figure 6.

Figure 6 Expected value of perfect information



The total population EVPI using the estimates of 11,498 children in England and Wales using a £20,000 per QALY threshold is £34,697,442. This is the value of resolving the uncertainty in the model. Therefore, this indicates that research is valuable in this area. The EVPPI results in Figure 7 indicate where this research should be prioritised.

Figure 7 Expected value of perfect parameter information for diagnosing food allergies in children



These results indicate that research is valuable into the majority of the variables in the analyses; however, the specificity of the tests appears to warrant significant investment. This is because the distribution varies significantly from 20% up to 90%. This is consistent with the deterministic sensitivity analysis where these factors made the largest impact. It is also the factor that could decide between the two tests. The quality of life for no allergy is in fact likely to be linked to the difference between allergy and no allergy, with smaller differences resulting in higher ICERs. Therefore, the quality of life of people with allergies compared to no allergies would be a useful area or research.

Limitations

Poor quality of the clinical information

The model must be viewed as purely exploratory given the very poor information available on the treatment pathway and the natural history. The clinical data underpinning the model was not based on systematic reviews and was therefore, a rather arbitrary selection of available evidence sources.

The diagnostic studies were of low quality and therefore, the estimates of sensitivity and specificity are associated with considerable uncertainty. However, this should have been captured in the probabilistic sensitivity analysis.

The modeling of long term outcomes was based on the little information available and resource constraints. Therefore, important factors that could affect the cost effectiveness could have been excluded.

The quality of life values are relatively robust given the difficulty of collecting quality of life data in this population. However, the data was collected in a older population (12 year olds) than the tested population.

Population

The model only considered one population rather than the range of IgE-mediated allergies. Therefore, there are issues with transferability to other populations that need to be considered. In this case it should be transferable the main sources of uncertainty are the initial age of diagnosis, rate of desensitization, sensitivity and specificity of the tests. However, these are unlikely to affect the cost effectiveness of the tests, but the way the tests are used and possibly the downstream management of the condition. Therefore, the cost effectiveness results should be transferable to other allergies.

Treatment of allergies

The management of allergies in the model is a very simplified version of what happens in reality. Therefore, the reassessments and treatments such as sensitization of allergies and the proper modeling of epinephrine-pens are not included. The impact of these issues on the cost effectiveness of testing is unclear since if it is more expensive than currently modeled then the value of more accurate diagnosis could be more value. Alternatively if it increases the rate of desensitization than the value of testing may be less than modeled. However, it appears that the more expensive management is then the mode cost effective testing becomes.

Discussion and conclusion

The results from this analysis appear to suggest that skin prick and IgE blood testing to confirm a diagnosis of food allergy in children is associated with ICERs below a threshold of £20,000 per QALY gained. The difference in quality of life between those with allergies and those without appears to be the main driver behind the cost effectiveness. Sensitivity analyses indicate that this decision is robust with very high probabilities of being cost effective. The skin prick test appears to be the most cost effective option; however this is likely to depend on the number of people tested per year to make sure that wastage does not occur.

The analysis is very simplistic in terms of the model structure and the data inputted into the model. Therefore, these results should be approached with caution. The full impact of allergies on individuals and the health service are not captured fully by the analysis. Nutritional well being of the child and the impact of repeat appointments from concerned parents are not comprehensively captured by the analysis. It is unclear in which way these factors would affect the cost effectiveness estimates.

Future work should concentrate on a more sophisticated representation of the management of food allergies after diagnosis including management techniques and retesting. In addition, it should be based on a full review of the available data.

Another area that would warrant further work is to examine the effect of diagnosing allergies in a realistic population, where there are a number of different allergies present. This could then determine whether there is one test that can be used for diagnosing all allergies or if both are required.

In conclusion, testing for food allergies appears to be a cost effective use of resources. However, further work is required to fully capture the potential benefits and costs of testing.

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