Appendix G: Full health economics report

The original health economic modelling we undertook for this guideline addressed 3 topics: active case-finding in populations at increased risk of coeliac disease (full guideline section 4.4), serological diagnosis of coeliac disease (full guideline sections 5.1 and 5.2) and dietitian-led follow-up of people with coeliac disease (full guideline section 5.4). Because modelling for active case-finding and dietitian-led follow-up was based on modified versions of the model developed for serological diagnosis, questions are presented out of guideline order, here: we describe the serological diagnosis model first (section G.1) and describe the ways in which it was modified for other questions in sections G.1.3.10 and G.2.4.

G.1 Serological diagnosis of coeliac disease (full guideline sections 5.1 and 5.2)

G.1.1 Decision problem

Table 1: Research questions

RQ4	1. Which serological test is the most appropriate to diagnose coeliac disease? 2. Depending on test results, should more than one test be used, and if so, what should be the sequence of testing?

Table 2: PICO

Population	Patients presenting with symptoms
Intervention	Individual or sequences of serological tests.
Comparator	Alternative testing strategies.
Outcomes	Cost–utility analysis based on the quality of life (in quality adjusted life years[QALYs]) and costs of correctly diagnosing and failing to diagnose coeliac disease.

G.1.2 Systematic review of published cost–utility analyses

G.1.2.1 Methods

Inclusion and exclusion criteria

The economic literature review aimed to identify economic evaluations in the form of cost–utility analyses exploring the costs and effects of different serological strategies to test for coeliac disease.

Search strategy

The search strategy was based on that used to identify clinical evidence for this question, with the RCT filter removed and a standard economic filter applied (see appendix C).

G.1.2.2 Results

Study identification

The search returned 135 studies; after title and abstract screening, we ordered the full texts of 10 studies. On perusal of the retrieved papers, no cost–utility analyses comparing serological testing strategies to diagnose coeliac disease could be included.

G.1.2.3 Discussion

Due to the lack of published economic evaluations to provide guidance to answer the review question, a de novo health economic model was proposed. The GDG identified that this was a high priority area for original health economic analysis.

G.1.3 Original cost–utility model – methods

G.1.3.1 Overview of the model

Table 3: Modelled population(s) and intervention(s)

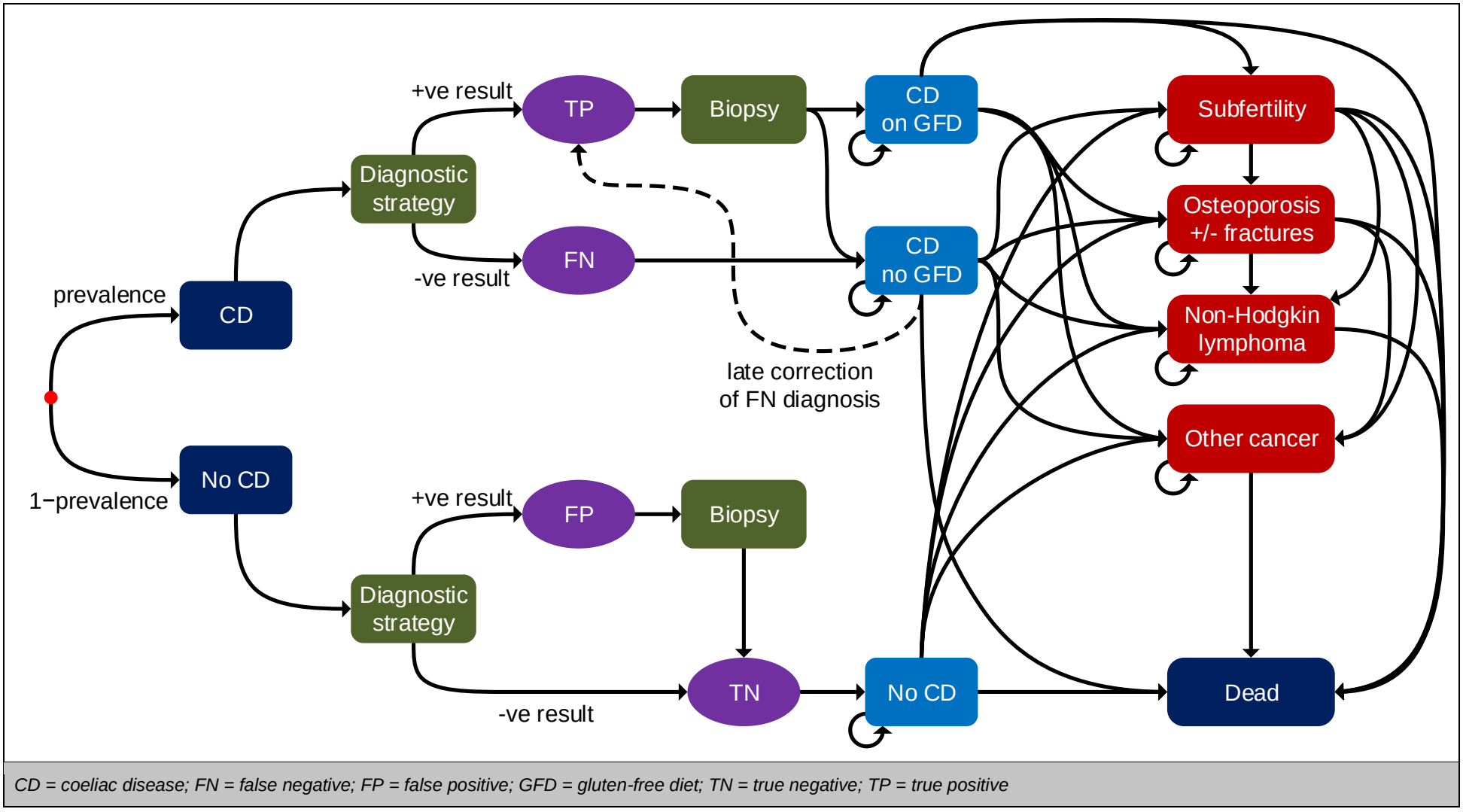
Population	Adults and children with symptoms suggestive of coeliac disease
Intervention	Individual tests or testing strategies including multiple tests for diagnosing coeliac disease
Comparator	Alternative tests or strategies.
Outcomes	A cost-utility analysis was constructed based on the quality of life (in quality adjusted life years[QALYs]) and costs of diagnosing coeliac disease.

We built a Markov model with annual cycles and a lifetime horizon. The Markov structure allows costs and utilities to be accrued for each year spent in a series of health states.

The tests and testing strategies included in the model are limited to those for which clinical evidence was available in the literature. The model draws on literature relevant to the adult or child population on which the analysis is being conducted.

The model uses a patient perspective for outcomes and an NHS/PSS perspective for costs, in line with the Guidelines Manual (2012).

Figure 1 provides a schematic depiction of the model structure.



CD = coeliac disease; FN = false negative; FP = false positive; GFD = gluten-free diet; TN = true negative; TP = true positive

Figure 1: Schematic representation of the original cost–utility model

The model represents a population with symptoms suggestive of coeliac disease. The initial branches in the decision tree separate the population into those with and without a true coeliac disease diagnosis. This means regardless of the outcome of the testing strategy, the model 'knows' the true diagnosis of the individuals. This enables risk factors associated with true presence of disease to be allocated appropriately.

The first stage models the probability of a selected diagnostic test or testing strategy generating positive and negative results for coeliac diagnosis. Those individuals with a positive test result progress to an endoscopy and biopsy to have their coeliac diagnosis confirmed. In the base case, we assume that biopsy is perfectly accurate at distinguishing a coeliac diagnosis. Those with a positive diagnosis then have a probability of adhering to a GFD with this then driving the risk factors as defined for treated and untreated coeliac disease. Those with a negative diagnosis continue to experience a symptomatic quality of life. There is a chance of late detection each year for those individuals with a false-negative diagnosis. There is also a hypothetical chance of correcting a false-positive diagnosis in the model; however, in the base case, biopsy for people with positive serology will correct any false-positive diagnosis, so the false positive correction only comes into play in strategies in which biopsy does not occur for all individuals.

During any model cycle the patient can develop osteoporosis, subfertility, cancer (divided into non-Hodgkin's lymphoma and other cancer) or die from other causes. The risk of each of these complications is stratified by whether the individual has treated (GFD-adherent true positives), untreated (non-GFD-adherent true positives plus all false negatives) or is without coeliac disease (all true negatives plus all false positives). The health states which represent the long-term consequences of coeliac disease capture the health-related quality of life and costs of each of the complications.

Key assumptions

There are a number of assumptions built into the economic model. These are summarised in Table 4.

Table 4: Key assumptions of original cost–utility model

The initial population have symptoms suggestive of coeliac disease.
All health states are mutually exclusive.
Health outcomes and costs are discounted at a rate of 3.5% in line with the NICE reference case.
Estimated distributions for each of the point parameter values have been applied to enable the uncertainty in each estimate to be quantified and included within estimates of cost-effectiveness.
Gluten-free diet adherence has a direct relationship with the risk of long-term complication development.

G.1.3.2 Parameters – general approach

Identifying sources of parameters

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

We asked the GDG to identify papers of relevance. During the systematic review we retrieved articles that did not meet the formal inclusion criteria, but appeared to be promising sources of evidence for our model. We studied the reference lists of articles retrieved through any of these approaches to identify any further publications of interest.

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

Selecting parameters

Our overriding selection criteria were as follows:

- The selected studies should report outcomes that correspond as closely as possible to the health states and events simulated in the model.
- The selected studies should report a population that closely matches the UK population (ideally, they should be drawn from the UK population).
- All other things being equal, more powerful studies (based on sample size and/or number of events) were preferred.
- Where there was no reason to discriminate between multiple possible sources for a given parameter, we gave consideration to quantitative synthesis (meta-analysis), to provide a single summary estimate.
- In the absence of any published evidence for a given parameter necessary to represent the treatment pathway, the GDG provided estimates to inform the parameterisation of the model.

G.1.3.3 Parameters – baseline characteristics

Coeliac disease prevalence

We based the prevalence of coeliac disease among a population with symptoms suggestive of coeliac disease on Hopper et al. (2008).

Cohort characteristics

The age of the cohort at baseline is an assumption with 30 being used for the adult population and 5 used when the cohort begins in childhood.

The sex split of the model is based on a 2:1 female:male ratio that was used when the model was built for the previous coeliac disease guideline (CG86).

Gluten-free diet adherence

The model assumes that the rate of compliance with a gluten free diet is 65.7% in adults. This value was based on evidence from Wylie et al. (2005), as used in our exploration of dietitian-led follow-up (see G.3). As this guideline recommends that access to specialist dietetic support should be available in the follow-up of people with coeliac disease (see full guideline, section 5.4), it makes sense that modelled GFD adherence should reflect our best estimate of the level of adherence that can be expected under those circumstances. It also accords relatively well with the value of 60% used in the model for CG86 (Dretzke et al. 2004).

For children, we used an adherence probability of 84%, drawn from a study by Kinos et al. (2012). This source had the advantage of specifically reporting adherence in children who had been symptomatic at the point of diagnosis (and comparing it with adherence rates

achieved by children who were screen-detected, which is useful for our case-finding model – see section G.2.3.3, below).

G.1.3.4 Parameters – diagnostic accuracy

The sensitivity and specificity of the tests used to diagnose coeliac disease used in the model is drawn from the clinical evidence review. The 95% confidence intervals enable the uncertainty in the estimate of the accuracy of each of the tests to be quantified.

Due to the small number of studies which make up the underlying evidence-base for the diagnostic accuracy of each of the tests, correlations between sensitivity and specificity could not be estimated. We recognise that, in reality, these parameters are likely to be correlated; however, the degree of association can only be quantified if several studies are available, and this was not the case, in this instance. As a result, we effectively assume that the sensitivity and specificity of each test are independent. This is a limitation which results in suboptimal sampling of the diagnostic accuracy of each test in probabilistic sensitivity analysis.

Table 5 and Table 6 give abbreviations used in this document for the various testing strategies.

Table 5: Abbreviations used for strategies – adults

Abbreviation	Definition
IgADGP	IgA DGP
IgGDGP	IgG DGP
IgAEMA	IgA EMA
IgATTG	IgA tTG
IgGDGP+IgAEMA	Positive on both IgG DGP + IgA EMA
IgGDGP+IgATTG	Positive on both IgG DGP + IgA tTG
IgGDGP+IgADGP+IgAEMA	Positive on all 3 of IgG DGP + IgA DGP + IgA EMA
IgGDGP+IgADGP+IgATTG	Positive on all 3 of IgG DGP + IgA DGP + IgA TTG
IgGDGP+IgAEMA+IgATTG	Positive on all 3 of IgG DGP + IgA EMA + IgA tTG
IgGDGP+IgADGP+IgAEMA+IgATTG	Positive on all 4 of IgG DGP + IgA DGP + IgA EMA + IgA TTG
BothIgATTG+IgAEMA	Positive on both IgA tTG + IgA EMA (IgA EMA undertaken in all cases)
StepIgATTG_then_IgAEMA	Positive on both IgA tTG + IgA EMA (IgA EMA only undertaken if IgA tTG is positive)
EitherIgATTG+IgAEMA	Positive on either IgA tTG or IgA EMA
StepIgATTG_equiv_then_IgAEMA	Strongly positive on IgA TTG or weakly positive on IgA TTG and positive on IgA EMA

Table 6: Abbreviations used for strategies – children

Abbreviation	Definition
IgADGP	IgA DGP
IgAEMA	IgA EMA
IgATTG	IgA tTG
IgGDGP	IgG DGP
IgGDGP+IgAEMA	Positive on both IgA DGP + IgA EMA
IgGDGP+IgATTG	Positive on both IgA DGP + IgA tTG
IgGDGP+IgADGP+IgAEMA	Positive on all 3 of IgG DGP + IgA DGP + IgA EMA
IgGDGP+IgADGP+IgATTG	Positive on all 3 of IgG DGP + IgA DGP + IgA TTG
IgGDGP+IgAEMA+IgATTG	Positive on all 3 of IgG DGP + IgA EMA + IgA TTG
IgGDGP+IgADGP+IgAEMA+IgATTG	Positive on all 4 of IgG DGP + IgA DGP + IgA EMA + IgA TTG
HLA	HLA DQ2/DQ8 genotyping
IgATTG+IgAEMA+HLA	Positive on all 3 of IgA EMA + IgA TTG + HLA DQ2/DQ8 genotyping

G.1.3.5 Parameters – long-term complications of coeliac disease

Evidence on the potential long-term complication of coeliac disease was reviewed as part of question 1c. This evidence was discussed with the GDG, who then prioritised key areas on which we could focus to represent the potential costs and benefits of obtaining a diagnosis of coeliac disease. The risk of developing these complications is dependent on whether the coeliac disease is treated or untreated. Therefore, individuals with undiagnosed coeliac disease have the same risk of complications as those who are diagnosed but who are not adhering to a GFD. There are no specific risks of complications in children represented within the model.

The following section presents the evidence used to quantify the risk of long-term complications of coeliac disease for the treated and untreated groups separately.

Untreated Coeliac Disease

The risk of developing complications given untreated coeliac disease is sourced from the evidence collected as part of the review of the long-term consequences of undiagnosed or untreated coeliac disease (see full guideline, section 4.3). The variability in the evidence base prevented synthesis; therefore it was necessary for us to identify and individual source for each parameter. Evidence from a UK population was favoured, where available, with population size another key factor considered in study selection.

- Osteoporosis

  We restrict the development of osteoporosis to individuals over the age of 50 in line with NICE clinical guideline (CG146). The probability of developing osteoporosis in the general population is taken from estimates of the prevalence of osteoporosis in 50 and 80 year-olds, as detailed in the NICE technology appraisal of bisphosphonates [TA160]. We then fit a linear regression to these points to estimate the prevalence of osteoporosis at different ages.

  Godfrey et al. (2010) tested blood samples for coeliac disease and compared the medical records of those with positive coeliac serology with seronegative individuals. They found more of the group with undiagnosed coeliac disease developed osteoporosis.

- Subfertility

  In our model only individuals between the ages of 16 and 42 can develop and be treated for fertility problems.

The risk of subfertility in the untreated coeliac population is estimated from the evidence in the Hogen Esch et al. (2011) study. The prevalence of coeliac disease among a population of Dutch couples attending a fertility clinic was estimated and compared with that of the general population.

- Cancer risk

Silano et al. (2007) used data from the Italian Registry of the complications of coeliac disease, compared this with WHO Globoscan data, and looked for incidences of malignancy before or at the time of coeliac disease diagnosis.

  - NHL

    The probability that cancer is NHL is estimated from national cancer statistics data (ONS 2011). The ICD10 codes of each type of cancer are recorded and we have used this to estimate that chance that an incidence of cancer is NHL.

  - Other cancer

    In order to estimate quality of life and resource use for individuals who develop cancer we needed to select an appropriate proxy. The best proxy would be one that commanded an average amount of resources (in terms of diagnosis and treatment) and had an average quality of life for cancer. This is obviously difficult to locate in practice. We discussed the options available to us with our clinical adviser and the GDG and decided to represent all cancer with the costs and quality of life associated with colorectal cancer. The risk of developing other cancer remains more general.

Treated coeliac disease

- Osteoporosis

Ludvigsson et al. (2007) used Swedish National Board of Health data which identified a population of people with a coeliac disease diagnosis on discharge from hospital and compared this group with a control group matched on a number of characteristics including age and the year in which the discharge from hospital was made. The risk reported is subsequent fractures of any type; however, we use this to estimate the development of osteoporosis within the model which then has additional risks of fractures attributed, specified by fracture site.

- Subfertility

No evidence of an increased risk of sub-fertility could be found for individuals with coeliac disease adhering to a gluten-free diet; therefore, this group has the same risk of subfertility as the non-coeliac populations in the model.

- Cancer risk

The risk of cancer in a treated coeliac disease population is represented by the evidence reported by Goldacre et al. (2008), based on a retrospective analysis of UK medical records data. The population considered were patients admitted to hospital with coeliac disease who later developed cancer. We are interested in the risk of developing any malignancy and in this study the control group which represented population cancer risk was devised from medical records of individuals who were hospitalised for medical conditions other than ulcerative colitis, Crohn's disease and coeliac disease. An alternative study was available by Grainge et al. (2012) study in which a population with diagnosed coeliac disease were monitored for the development of cancer.

- NHL

  The same probability that cancer is NHL is used as in the population with untreated coeliac disease, as described above.

Delay to diagnosis

People with coeliac disease in the UK may not always have their disease diagnosed immediately. Sanders et al. (2002) looked at incidence rates of CD in South Yorkshire. They found a median duration of symptoms before diagnosis of 4.9 years. This delay to diagnosis is operationalised in the model through a delay in the length of time it takes for individuals with a false-negative diagnosis to receive a correct coeliac disease diagnosis, with the uncertainty in this estimate tested in sensitivity analysis.

Mortality

Age- and sex-specific estimates of background mortality are taken from UK lifetables (ONS).

There is an additional risk of mortality due to hip fracture (secondary to osteoporosis), NHL or other cancer. No other risks of mortality related to coeliac disease were identified in the literature.

G.1.3.6 Parameters – resource use and costs

The healthcare resource use associated with symptoms suggestive of coeliac is dependent on the presence of coeliac disease and their diagnosed state and is based on a study by Violato et al. (2012). This is an analysis of the GPRD database for information on resource use both before and after coeliac diagnosis and in comparison to a control group. The resource use is analysed within the paper in four categories: consultations, tests, outpatient referrals and prescriptions. The consultations category includes the count of contact days per individual with a number of healthcare professionals including GP, nurse, physiotherapist, counsellor etc. The use of contact days as the defining metric, means that multiple consultations in one day results in a single entry in the dataset that day. The tests category includes electrolytes, blood count and liver function tests, for example. Other tests such as measuring weight and blood pressure were assumed to constitute part of a normal consultation and therefore did not carry any additional cost. The ‘outpatient referrals’ category is specifically concerned with appointments at consultant-led outpatient clinics, with attendance at A&E excluded. Some specialties are excluded from the calculations such as obstetrics, genitourinary, x-ray and pathology due to large variations over time in the way in which different GPs can record referrals.

The prescriptions for each patient were categorised into each of the BNF chapters, with a ‘Miscellaneous’ category to include those products such as food supplements that did not conform to the BNF categorisation. This enabled elements of the prescription costs to be excluded from our calculations where they are accounted for elsewhere within the model. This is relevant to the musculoskeletal and joint disease category, for which the cost of drugs used to treat osteoporosis are included for the patients in the model who develop osteoporosis as a complication of coeliac disease, and also the food supplements category for which the cost of gluten-free foods is calculated from data on the number of prescribed items. The cost of each of the resource use category as detailed in the study was inflated to current prices using the HCHS prices indices.

The resource use associated with the long-term complications is based on published evidence specific to each of the complications considered. The values used and their sources are detailed in Table 7.

- Osteoporosis

  The resource use associated with osteoporosis diagnosis is included within the Violato et al. (2012) estimates. The use of pharmacological treatment for osteoporosis however is calculated from the prescription pricing database (Dec, 2013) in which the proportion prescribed in each practice of each of the fracture prevention drugs recommended by NICE is detailed. We then take prices from the NHS Drug Tariff (April, 2014) and calculate a weighted average cost of bisphosphonate prescriptions by the proportions of each of the drugs prescribed.

- Subfertility

  The resource use associated with sub-fertility is estimated from the NICE guideline on Fertility (CG156). Between the ages of 16 and 40, 3 rounds of IVF treatment are offered, with a chance of a live birth at each stage. For individuals over 40, only 1 round of fertility treatment is offered.

Costs

Where resource use estimates have been obtained from the literature, NHS reference costs (2012/2013) have been allocated to represent the cost to the healthcare system. Costs derived directly from published evidence have been inflated to the same year for consistency.

Diagnostic test costs

National average unit costs for serological and genetic tests are not available and therefore an alternative source was needed.

The costs of the tests conducted by a number of laboratories were provided and from this an average cost for each test was generated along with an estimate of the uncertainty around this value. Therefore although the averages produced may not be perfectly representative of the national average, the ability to estimate some uncertainty in these estimates within the modelling framework allows some confidence to be placed in any results based on these figures.

The cost of each diagnostic strategy were estimated by adding the cost of each individual test within any given strategy.

Endoscopy and biopsy

NHS reference costs were used to represent the cost of an endoscopy and biopsy to diagnose coeliac disease. The cost is greater in children as a general anaesthetic is necessary in order to perform the procedure, which is not the case in adults. Therefore the cost of the endoscopy within the model is age-dependent.

Gluten-free diet

In order to conform to the NHS and PSS perspective for costs (Guidelines Manual 2012), the cost of a gluten-free diet is limited to those products available on prescription. In line with the methods used in CG86, we estimated the total cost to the NHS of GFD prescriptions and divided it by an estimate of the total number of people with diagnosed coeliac disease in England and Wales to generate an annual cost of a GFD per person. We used Prescription Cost Analysis data from HSCIC (2014) for the NHS cost of gluten-free prescriptions, ONS(2013) data on the total population of England and Wales and an estimate of coeliac disease incidence from Fowell et al. (2006).

Long-term consequences

The cost of each of the fractures and death due to a hip fracture is estimated by inflating the values reported in the HTA on the treatment of established osteoporosis by Kanis et al. (2002). The costs used in this economic evaluation were taken from a study by Dolan and Torgerson (1998) aimed at estimating the cost of osteoporotic fractures in women in the UK.

G.1.3.7 Parameters – costs of introducing new tests

The GDG noted that current provision of serological testing is variable, with different laboratories relying on different assays, either singly or in combination. This means that, in order to recommend the routine use of any particular strategy (especially one involving more than 1 test), it would be necessary to take account of the implications for standardising practice. In particular, the additional costs associated with the new equipment required by some laboratories should be accounted for. Therefore, in addition to the unit cost of each test, the original model included an estimate of additional capital costs that would be incurred, by some laboratories, in expanding their provision to enable them to undertake those tests. Preliminary analysis in the adult population indicated that strategies involving testing with IgA tTG or EMA were likely to offer the best value for money and therefore, as an example, we explored the potential resource use and cost implications of laboratories having to purchase new equipment and change their practices in order to perform the tests that may be recommended. Data from a national audit of current provision (NEQAS) were used to estimate the proportion of laboratories for which such additional investment would be necessary.

In order to appropriately represent the implications of new strategies for diagnostic testing, we were concerned with the current provision of tTG and EMA tests in the NHS, the number of tests conducted each year by the labs and the capital costs of any new equipment necessary to offer a different test. This information is not widely available and therefore we relied on the opinion of experts to be able to estimate these parameters. The values, along with estimates of their uncertainty, are detailed in Table 7

G.1.3.8 Parameters – quality of life

We conducted a literature search to locate utility values to be applied to the health states within the economic model.

The quality of life associated with coeliac disease is based on the best available evidence from a systematic review of studies measuring quality of life with EQ-5D or SF-36.

Usai et al. (2007) was the primary source for estimates of quality of life associated with the model's main health states. This was an Italian study that evaluated the effect of IBS-type symptoms and adherence to a gluten free diet on the quality of life of a population of individuals with coeliac disease and a control group. Quality of life was assessed using the SF-36 which we mapped onto the EQ-5D scale using a published and well recognised mapping algorithm (Ara & Brazier, 2008).

Because this question is concerned with a population of people with symptoms suggestive of coeliac disease, we only used the values relating to people who entered the study with symptoms. We distinguished between people with coeliac disease on a GFD, people with CD but not on a GFD (whether due to lack of adherence or false-negative diagnosis) and people without coeliac disease, and estimated the proportional decrement associated with each by comparing these values with the HRQoL of asymptomatic controls without coeliac disease.

The model applies a decrement in utility to anyone undergoing an endoscopy. In the absence of any direct evidence on the topic, the impact of the procedure is assumed to be equivalent to the loss of 1 quality-adjusted life-day.

We obtained the utility values for the complications represented in the model from a number of sources, as detailed in Table 7. The model applied the quality of life impacts of these additional complications multiplicatively. Although it is only possible to enter the subfertility states of the model at certain ages (between 16 and 42), the model assumed that the utility decrement associated with subfertility is lifelong. The model assumes that there is no decrement to quality of life in individuals with osteoporosis without a fracture (Peasgood et al., 2009). The quality of life of individuals who have a vertebral or wrist fracture is diminished for the year in which the fracture occurs; however, quality of life is reduced for the remainder of the individual's life after a hip fracture.

G.1.3.9 Parameters – summary

Table 7 provides details of all parameters used in the model, including the distributions and parameters used in probabilistic sensitivity analysis (see G.1.3.10).

Table 7: Model parameters

Parameter	Value (95%CI)	Distribution and parameters	Source
Diagnostic accuracy (adults)			
Sensitivity			
IgAEMA	0.85 (0.79, 0.90)	Beta: α=114.8; β=20.3	Clinical review meta-analyses
IgATTG	0.91 (0.85, 0.95)	Beta: α=113.6; β=11.2	
IgADGP	0.83 (0.72, 0.92)	Beta: α=44.2; β=9.0	
IgGDGP	0.83 (0.71, 0.92)	Beta: α=40.0; β=8.2	
IgGDGP+IgATTG	0.72 (0.64, 0.79)	Beta: α=98.4; β=38.3	
IgGDGP+IgAEMA	0.73 (0.66, 0.80)	Beta: α=112.1; β=41.5	
IgGDGP+IgADGP+IgATTG	0.73 (0.66, 0.80)	Beta: α=112.1; β=41.5	
IgGDGP+IgADGP+IgAEMA	0.58 (0.50, 0.66)	Beta: α=84.2; β=61.0	
IgGDGP+IgAEMA+IgATTG	0.70 (0.62, 0.78)	Beta: α=87.5; β=37.5	
IgGDGP+IgADGP+IgAEMA+IgATTG	0.56 (0.48, 0.64)	Beta: α=82.3; β=64.6	
StepIgATTG_equiv_then_IgAEMA	0.86 (0.77, 0.93)	Beta: α=61.3; β=10.0	
StepIgATTG_then_IgAEMA	0.87 (0.67, 0.98)	Beta: α=13.9; β=2.1	
BothIgATTG+IgAEMA	0.85 (0.71, 0.95)	Beta: α=25.8; β=4.6	
EitherIgATTG+I	0.92 (0.85, 0.97)	Beta: α=71.3; β=6.2	
Specificity			
IgAEMA	0.98 (0.97, 0.98)	Beta: α=2950.5; β=60.2	Clinical review meta-analyses
IgATTG	0.91 (0.90, 0.92)	Beta: α=2862.1; β=283.1	
IgADGP	0.80 (0.71, 0.88)	Beta: α=67.3; β=16.8	
IgGDGP	0.97 (0.94, 0.99)	Beta: α=172.5; β=5.3	
IgGDGP+IgATTG	0.96 (0.86, 1.00)	Beta: α=24.2; β=1.0	
IgGDGP+IgAEMA	0.95 (0.91, 0.98)	Beta: α=140.6; β=7.4	
IgGDGP+IgADGP+IgATTG	0.99 (0.98, 1.00)	Beta: α=375.5; β=3.8	
IgGDGP+IgADGP+IgAEMA	0.99 (0.98, 1.00)	Beta: α=375.5; β=3.8	
IgGDGP+IgAEMA+IgATTG	0.99 (0.98, 1.00)	Beta: α=375.5; β=3.8	

Parameter	Value (95%CI)	Distribution and parameters	Source
IgGDGP+IgADGP+IgAEMA+IgATTG	0.99 (0.98, 1.00)	Beta: α=375.5; β=3.8	
StepIgATTG_equiv_then_IgAEMA	0.99 (0.98, 0.99)	Beta: α=1505.0; β=15.2	
StepIgATTG_then_IgAEMA	0.97 (0.95, 0.98)	Beta: α=481.0; β=14.9	
BothIgATTG+IgAEMA	0.99 (0.98, 1.00)	Beta: α=375.5; β=3.8	
EitherIgATTG+I	0.90 (0.88, 0.91)	Beta: α=1382.0; β=153.6	
Diagnostic accuracy (children)			
Sensitivity			
IgAEMA	0.97 (0.94, 0.99)	Beta: α=172.5; β=5.3	Clinical review meta-analyses
IgATTG	0.96 (0.93, 0.98)	Beta: α=156.4; β=6.5	
IgADGP	0.82 (0.73, 0.90)	Beta: α=63.5; β=13.9	
IgGDGP	0.89 (0.80, 0.95)	Beta: α=58.6; β=7.2	
HLA	0.99 (0.96, 1.00)	Beta: α=93.1; β=0.9	
IgGDGP+IgATTG	0.83 (0.71, 0.92)	Beta: α=40.0; β=8.2	
IgGDGP+IgAEMA	0.72 (0.64, 0.79)	Beta: α=98.4; β=38.3	
IgGDGP+IgADGP+IgATTG	0.73 (0.66, 0.80)	Beta: α=112.1; β=41.5	
IgGDGP+IgADGP+IgAEMA	0.73 (0.66, 0.80)	Beta: α=112.1; β=41.5	
IgGDGP+IgAEMA+IgATTG	0.58 (0.50, 0.66)	Beta: α=84.2; β=61.0	
IgGDGP+IgADGP+IgAEMA+IgATTG	0.70 (0.62, 0.78)	Beta: α=87.5; β=37.5	
IgATTG+IgAEMA+HLA	0.99 (0.96, 1.00)	Beta: α=93.1; β=0.9	
Specificity			
IgAEMA	0.76 (0.68, 0.84)	Beta: α=82.4; β=26.0	Clinical review meta-analyses
IgATTG	0.86 (0.79, 0.92)	Beta: α=93.3; β=15.2	
IgADGP	0.86 (0.78, 0.93)	Beta: α=69.9; β=11.4	
IgGDGP	0.81 (0.72, 0.89)	Beta: α=65.5; β=15.4	
HLA	0.69 (0.59, 0.79)	Beta: α=56.0; β=25.2	
IgGDGP+IgATTG	0.97 (0.94, 0.99)	Beta: α=172.5; β=5.3	
IgGDGP+IgAEMA	0.96 (0.86, 1.00)	Beta: α=24.2; β=1.0	
IgGDGP+IgADGP+IgATTG	0.95 (0.91, 0.98)	Beta: α=140.6; β=7.4	

Parameter	Value (95%CI)	Distribution and parameters	Source
IgGDGP+IgADGP+IgAEMA	0.99 (0.98, 1.00)	Beta: α=375.5; β=3.8	
IgGDGP+IgAEMA+IgATTG	0.99 (0.98, 1.00)	Beta: α=375.5; β=3.8	
IgGDGP+IgADGP+IgAEMA+IgATTG	0.99 (0.98, 1.00)	Beta: α=375.5; β=3.8	
IgATTG+IgAEMA+HLA	0.96 (0.91, 0.99)	Beta: α=87.5; β=3.6	
Prevalence			
Ln[odds] of CD in modelled populations:			
Symptomatic presenters	-3.18 (-3.40, -2.95)	Normal: μ=-3.18; σ=0.12	Hopper et al. (2008)
Prevalence of CD in modelled populations:			
Symptomatic presenters	4.0%		Calculated
Adherence to GFD			
Probability of adhering to GFD (adults)	0.657 (0.561, 0.746)	Beta: α=65; β=34	Wylie et al. 2005
Probability of adhering to GFD (symptomatic children)	0.840 (0.758, 0.909)	Beta: α=74; β=14	Kinos et al. 2012
General			
Median time to detection of CD in undiagnosed people	4.9 (3.4, 6.5)	Triangular: min=3.0; mode=4.9; max=7.0	Sanders et al. (2002)
Probability of late detection of CD after FN diagnosis	0.132		Calculated
Median time to exclusion of CD in FP diagnoses	15.0 (7.2, 22.8)	Triangular: min=5.0; mode=15.0; max=25.0	Assumption
Probability of late exclusion of CD after FP diagnosis	0.045		Calculated
Long-term complications			
Cancer			
Incidence ratio -v- general population			
CD on GFD	1.16 (0.92, 1.46)	Lognormal: μ=0.15; σ=0.12	Goldacre et al. (2008)
CD not on GFD	1.30 (1.00, 1.69)	Lognormal: μ=0.26; σ=0.14	Silano et al. (2007)
Probability cancer is NHL			
General population	0.03 (0.02, 0.03)	Beta: α=40.70; β=1560.31	ONS (2011)
CD on GFD	0.10 (0.05, 0.17)	Beta: α=9; β=82	
CD not on GFD	0.36 (0.24, 0.49)	Beta: α=20; β=35	

Parameter	Value (95%CI)	Distribution and parameters	Source
Sub-fertility			
OR CD not on GFD -v- general population	1.38 (0.47, 4.05)	Lognormal: μ=0.32; σ=0.55	Hogen Esch et al. (2011)
Per-cycle probability of developing subfertility			
Proportion of gen. pop. experiencing subfertility	14.0%	Not varied in PSA	Fertility guideline (CG156)
General population	0.0056		Calculated
CD on GFD	0.0056		Calculated
CD not on GFD	0.0077		Calculated
Regression coefficients for prob of IVF success			
Constant	-0.641	Not varied in PSA	Estimated from data in fertility guideline (CG156)
Age	0.075		
Age^2	-0.001		
Osteoporosis			
HR_HipFracMort	1.87 (1.50, 2.32)	Lognormal: μ=0.63; σ=0.11	Goldacre et al. 2002
OR -v- general population			
CD on GFD	1.40 (1.30, 1.50)	Lognormal: μ=0.34; σ=0.04	Ludvigsson et al. (2007)
CD not on GFD	2.59 (1.32, 5.09)	Lognormal: μ=0.95; σ=0.34	Godfrey et al. (2010)
Per-cycle probability of developing osteoporosis			
Age <50			
Proportion of GP with osteoporosis at age 50	2.0%	Not varied in PSA	NICE TA160
General population	0.0004		Calculated
CD on GFD	0.0006		Calculated
CD not on GFD	0.0010		Calculated
Age 50+			
Proportion of GP with osteoporosis at age 80	25.0%	Not varied in PSA	NICE TA160
General population	0.0089		Calculated
CD on GFD	0.0124		Calculated
CD not on GFD	0.0227		Calculated
Regression coefficients for prob of hip fracture			

Parameter	Value (95%CI)	Distribution and parameters	Source
Constant	0.0383	Not varied in PSA	Estimated from data in Kanis et al. (2002)
Age	-1.5E-3		
Age^2	1.6E-5		
Regression coefficients for prob of wrist fracture			
Constant	-0.0213	Not varied in PSA	Estimated from data in Kanis et al. (2002)
Age	8.1E-4		
Age^2	-5.2E-6		
Regression coefficients for prob of vertebral fracture			
Constant	-0.0185	Not varied in PSA	Estimated from data in Kanis et al. (2002)
Age	4.8E-4		
Age^2	-1.7E-6		
Raised probability of further # following hip #			
Hip	2.30 (1.29, 3.31)	Triangular: min=1.00; mode=2.30; max=3.60	Kanis et al. (2002)
Vertebral	2.50 (1.34, 3.66)	Triangular: min=1.00; mode=2.50; max=4.00	
Wrist	1.40 (1.09, 1.71)	Triangular: min=1.00; mode=1.40; max=1.80	
Excess mortality associated with coexisting conditions			
Type 1 diabetes			
Men			
0-35	4.90 (2.83, 8.49)	Lognormal: μ=1.59; σ=0.28	Soedamah-Muthu et al. (2006)
36-45	5.20 (3.09, 8.76)	Lognormal: μ=1.65; σ=0.27	
46-55	6.50 (4.08, 10.35)	Lognormal: μ=1.87; σ=0.24	
56-65	3.40 (2.31, 5.01)	Lognormal: μ=1.22; σ=0.20	
66-75	1.90 (1.22, 2.95)	Lognormal: μ=0.64; σ=0.23	
76+	1.60 (0.94, 2.73)	Lognormal: μ=0.47; σ=0.27	
Women			

Parameter	Value (95%CI)	Distribution and parameters	Source
0-35	6.90 (3.19, 14.94)	Lognormal: μ=1.93; σ=0.39	Soedamah-Muthu et al. (2006)
36-45	11.80 (4.91, 28.36)	Lognormal: μ=2.47; σ=0.45	
46-55	3.70 (2.22, 6.16)	Lognormal: μ=1.31; σ=0.26	
56-65	4.50 (2.88, 7.04)	Lognormal: μ=1.50; σ=0.23	
66-75	3.80 (2.30, 6.29)	Lognormal: μ=1.34; σ=0.26	
76+	3.10 (1.61, 5.95)	Lognormal: μ=1.13; σ=0.33	
Autoimmune thyroid disease			
Men	1.05 (0.86, 1.29)	Lognormal: μ=0.05; σ=0.10	Franklyn et al. (2005)
Women	1.16 (1.05, 1.28)	Lognormal: μ=0.15; σ=0.05	
Costs			
Unit costs for individual serological tests			
IgA_TTG	£11.04 (£7.22, £15.66)	Gamma: α=26.16; β=0.42	Personal communication with various laboratories offering CD testing in the UK.
IgA_EMA	£9.54 (£7.92, £11.30)	Gamma: α=122.57; β=0.08	
IgA_DGP	£11.67 (£6.55, £18.23)	Gamma: α=15.17; β=0.77	
IgG_DGP	£14.23 (£13.40, £15.09)	Gamma: α=1095.15; β=0.01	
HLA	£71.51 (£53.84, £91.65)	Gamma: α=54.79; β=1.31	
Additional cost of performing >1 test			
Capital cost of equipment for IgATTG	£12000 (£8894, £15106)	Triangular: min=£8000; mode=£12000; max=£16000	GDG estimate
Proportion of labs requiring new equipment for IgATTG	11.6% (6.7%, 17.7%)	Beta: α=15; β=114	NEQAS
Throughput of labs requiring new equipment for IgATTG	15,000 (7,236, 22,764)	Triangular: min=5,000; mode=15,000; max=25,000	Assumption
Total additional cost per case	£0.09		Calculated
Capital cost of equipment for IgAEMA	£12000 (£8894, £15106)	Triangular: min=£8000; mode=£12000; max=£16000	GDG estimate
Proportion of labs requiring new equipment for IgAEMA	38.0% (29.8%, 46.5%)	Beta: α=49; β=80	NEQAS
Throughput of labs requiring new equipment for	15,000 (7,236, 22,764)	Triangular: min=5,000;	Assumption

Parameter	Value (95%CI)	Distribution and parameters	Source
IgAEMA		mode=15,000; max=25,000	
Total additional cost per case	£0.30		Calculated
Proportion TTG+s in the 'equivocal' range	61.2% (51.4%, 70.6%)	Beta: α=60; β=38	Swallow et al. (2013)
Total serology costs			
Adults			
IgAEMA	£9.84		Calculated
IgATTG	£11.14		Calculated
IgADGP	£11.67		Calculated
IgGDGP	£14.23		Calculated
IgGDGP+IgATTG	£25.37		Calculated
IgGDGP+IgAEMA	£24.07		Calculated
IgGDGP+IgADGP+IgATTG	£37.03		Calculated
IgGDGP+IgADGP+IgAEMA	£35.73		Calculated
IgGDGP+IgAEMA+IgATTG	£35.21		Calculated
IgGDGP+IgADGP+IgAEMA+IgATTG	£46.87		Calculated
StepIgATTG_equiv_then_IgAEMA	£12.16		Calculated
StepIgATTG_then_IgAEMA	£12.61		Calculated
BothIgATTG+IgAEMA	£20.98		Calculated
EitherIgATTG+I	£19.80		Calculated
Children			
IgAEMA	£9.54		Calculated
IgATTG	£11.04		Calculated
IgADGP	£11.67		Calculated
IgGDGP	£14.23		Calculated
HLA	£71.51		Calculated
IgGDGP+IgATTG	£25.37		Calculated
IgGDGP+IgAEMA	£24.07		Calculated
IgGDGP+IgADGP+IgATTG	£37.03		Calculated

Parameter	Value (95%CI)	Distribution and parameters	Source
IgGDGP+IgADGP+IgAEMA	£35.73		Calculated
IgGDGP+IgAEMA+IgATTG	£35.21		Calculated
IgGDGP+IgADGP+IgAEMA+IgATTG	£46.87		Calculated
IgATTG+IgAEMA+HLA	£92.49		Calculated
Endoscopic biopsies			
Unit costs			
Adults	£443.13 (£422.35, £464.41)	Gamma: α=1705.26; β=0.26	NHS Reference Costs (2013/14)
Children	£814.38 (£737.24, £895.31)	Gamma: α=407.73; β=2.00	
Proportion of unreadable biopsies requiring repetition	0.018 (0.004, 0.042)	Beta: α=3; β=167	Clouzeau-Girard et al. (2010)
Total cost of biopsies			
Endoscopic biopsy (adults)	£450.95		Calculated
Endoscopic biopsy (children)	£828.75		Calculated
Gluten-free diet prescriptions			
Population of England	53,493,700	Not varied in PSA	ONS (2013)
Coeliac disease prevalence (general population)	0.26%	Not varied in PSA	Fowell et al. (2006)
Number diagnosed with coeliac disease in England	139,084		Calculated
Annual NHS spend on prescribed GFD products (England, 2013)	£27,015,942	Not varied in PSA	HSCIC (2014)
Annual cost of GFD prescriptions per person	£194.24 (£125.70, £277.46)	Gamma: α=25.00; β=7.77	Calculated (SE assumed 20% of mean)
Annual maintenance costs by diagnosis			
False negatives			
Consultations	£178.67 (£175.50, £181.87)	Gamma: α=12104.06; β=0.01	Violato et al. (2012)
Tests	£11.19 (£10.85, £11.53)	Gamma: α=4135.82; β=0.00	
Outpatient referrals	£39.82 (£38.26, £41.41)	Gamma: α=2446.87; β=0.02	

Parameter	Value (95%CI)	Distribution and parameters	Source
Prescriptions	£151.76 (£147.59, £155.99)	Gamma: α=5014.99; β=0.03	
Proportion of prescriptions bisphosphonates + GFD	5.7%	Not varied in PSA	Prescription Pricing Database (2013)
All positives (true and false)			
Consultations	£216.34 (£211.05, £221.69)	Gamma: α=6349.42; β=0.03	Violato et al. (2012)
Tests	£20.34 (£19.53, £21.16)	Gamma: α=2402.18; β=0.01	
Outpatient referrals	£484.34 (£472.52, £496.31)	Gamma: α=6366.83; β=0.08	
Prescriptions	£33.80 (£31.66, £36.01)	Gamma: α=923.90; β=0.04	
Proportion of prescriptions bisphosphonates + GFD	53.4%	Not varied in PSA	Prescription Pricing Database (2013)
True negatives			
Consultations	£12.38 (£12.21, £12.55)	Gamma: α=20722.61; β=0.00	Violato et al. (2012)
Tests	£144.23 (£142.95, £145.51)	Gamma: α=48784.84; β=0.00	
Outpatient referrals	£25.72 (£25.07, £26.38)	Gamma: α=5894.57; β=0.00	
Prescriptions	£174.36 (£171.76, £176.98)	Gamma: α=17109.35; β=0.01	
Proportion of prescriptions bisphosphonates + GFD	4.3%	Not varied in PSA	Prescription Pricing Database (2013)
Total annual maintenance costs			
TP	£496.27		Calculated
FN	£372.80		Calculated
FP	£496.27		Calculated
TN	£349.24		Calculated
Annual costs of long-term complications			
Sub-fertility (1 course IVF)	£3262.95 (£2111.61, £4660.81)	Gamma: α=25.00; β=130.52	Maheshwari et al. (2011) (SE assumed 20% of mean)

Parameter	Value (95%CI)	Distribution and parameters	Source
Treatment for NHL	£3164.13 (£2047.66, £4519.66)	Gamma: α=25.00; β=126.57	Ray et al. (2010) (SE assumed 20% of mean)
Lifetime cost for other cancer	£17146.43 (£11096.27, £24492.03)	Gamma: α=25.00; β=685.86	DoH (2011) (SE assumed 20% of mean)
Annual cost for other cancer	£1374.40		Calculated
Osteoporosis	£13.63 (£8.82, £19.47)	Gamma: α=25.00; β=0.55	Prescription Pricing Database (2013) (SE assumed 20% of mean)
Hip fracture	£11340.20 (£7338.78, £16198.39)	Gamma: α=25.00; β=453.61	Dolan and Torgerson (1998) (SE assumed 20% of mean)
Vertebral fracture	£712.79 (£461.28, £1018.15)	Gamma: α=25.00; β=28.51	
Wrist fracture	£800.16 (£517.82, £1142.95)	Gamma: α=25.00; β=32.01	
Utilities			
Symptomatic presenters			
Asymptomatic no CD	0.930 (0.815, 0.991)	Beta: α=27.07; β=2.04	Usai et al. (2007)
Symptomatic no CD	0.820 (0.733, 0.893)	Beta: α=71.18; β=15.62	
Symptomatic CD on GFD	0.720 (0.647, 0.788)	Beta: α=111.28; β=43.28	
Symptomatic CD no GFD	0.650 (0.585, 0.712)	Beta: α=139.35; β=75.03	
Decrement for symptoms	0.882		Calculated
Decrement for symptomatic CD (on GFD)	0.774		Calculated
Decrement for symptomatic CD (no GFD)	0.699		Calculated
Complications			
Subfertility (lifelong impact)	0.070 (0.063, 0.077)	Beta: α=371.93; β=4941.36	Scotland et al. (2011) (SE assumed 5% of mean)
NHL	0.618 (0.506, 0.724)	Beta: α=45.90; β=28.37	Ray et al. (2010)
Other cancer	0.580 (0.523, 0.636)	Beta: α=167.42; β=121.24	Ness et al. (1999) (SE assumed 5% of mean)
Hip fracture (1st year)	0.700 (0.015, 1.000)	Beta: α=0.64; β=0.27	Peasgood et al. (2009)

Parameter	Value (95%CI)	Distribution and parameters	Source
Hip fracture (subsequent years)	0.800 (0.643, 0.920)	Beta: α=24.29; β=6.07	
Vertebral fracture	0.590 (0.457, 0.716)	Beta: α=31.85; β=22.13	
Wrist fracture	0.956 (0.864, 0.997)	Beta: α=30.58; β=1.41	
Disutility associated with endoscopic biopsy	-0.003 (-0.005, -0.001)	Triangular: min=-0.005; mode=-0.003; max=0.000	Assumption
General population utility			
Men			
0-24	0.940 (0.918, 0.959)	Beta: α=470.31; β=30.02	Kind et al. (1999)
25-34	0.930 (0.912, 0.946)	Beta: α=779.51; β=58.67	
35-44	0.910 (0.888, 0.930)	Beta: α=659.28; β=65.20	
45-54	0.840 (0.803, 0.874)	Beta: α=341.41; β=65.03	
55-64	0.780 (0.740, 0.818)	Beta: α=333.84; β=94.16	
65-74	0.780 (0.743, 0.815)	Beta: α=388.47; β=109.57	
75+	0.750 (0.695, 0.801)	Beta: α=192.97; β=64.32	
Women			
0-24	0.940 (0.921, 0.956)	Beta: α=647.03; β=41.30	Kind et al. (1999)
25-34	0.930 (0.915, 0.944)	Beta: α=1137.28; β=85.60	
35-44	0.910 (0.892, 0.926)	Beta: α=1009.37; β=99.83	
45-54	0.850 (0.821, 0.877)	Beta: α=546.15; β=96.38	
55-64	0.810 (0.779, 0.839)	Beta: α=530.28; β=124.39	
65-74	0.780 (0.749, 0.810)	Beta: α=556.03; β=156.83	
75+	0.710 (0.672, 0.746)	Beta: α=412.39; β=168.44	

G.1.3.10 Sensitivity analyses

Deterministic sensitivity analyses

We analysed the impact of several key variables on model output. Particular emphasis was placed on the following:

- **Prevalence of coeliac disease** could potentially have an important effect on model dynamics and, therefore, was explored over a broad range.
- **Adherence to gluten-free diet** is another thing that could prove important in determining the relative desirability of different ways of diagnosing coeliac disease: if there is little prospect of true-positive diagnosis leading to effective treatment, then the value of correct diagnosis will be correspondingly reduced.
- **Late detection of coeliac disease** following a false-negative diagnosis is an important parameter that could attenuate the benefit of accurate diagnosis (that is, if cases are likely to come to light anyway, the benefit of detecting them on initial serology will be less). We did not find any directly relevant evidence to estimate this probability, so it was important to explore a range of possible values in our sensitivity analyses.
- **The cost of introducing new tests** was another important unknown in the model that was difficult to parameterise empirically (see G.1.3.7); therefore, we explored the implications of a wide range of plausible costs, from zero to £10 per test (the latter being many times greater than our best estimate of 9p [for IgA tTG] and 30p [for IgA EMA], as used in base-case analyses).

Probabilistic sensitivity analyses

We configured the models to perform probabilistic sensitivity analysis (PSA) to quantify uncertainty in the true values of input parameters. We specified probability distributions for all input variables, with bounds sourced from the study from which the value was obtained, where possible, or estimated based on the usual properties of data of that type.

PSA results are based on 1000 Monte-Carlo simulations, with parameter values drawn at random from the specified distributions. Table 7 provides details of each distribution and its parameters.

G.1.3.11 Scenario analysis

An exploratory analysis attempted to simulate the benefits, harms and costs of a diagnostic algorithm for children that enables a diagnosis of coeliac disease to be made without the need for confirmatory biopsy (as proposed by ESPGHAN). This analysis was more speculative than other simulated strategies, as it was not entirely based on direct evidence of the diagnostic accuracy of the algorithm; instead, it combined evidence on various tests (some of which had been used in isolation, in which case it was necessary to assume independence between them). Table 8 gives details of the additional parameters that were necessary to undertake this analysis.

Table 8: Additional parameters required to estimate ESPGHAN algorithm

Parameter	Value (95%CI)	Distribution and parameters	Source
Sensitivity of TTG10[a] given TTG+	0.80 (0.74, 0.84)	Beta: α=191; β=49	Nevoral et al. (2013)
Specificity of TTG10[a] given TTG+	0.76 (0.68, 0.84)	Beta: α=80; β=25	
Sensitivity of EMA given TTG+	0.97 (0.94, 0.99)	Beta: α=232; β=8	
Specificity of EMA given TTG+	0.40 (0.31, 0.49)	Beta: α=42; β=63	
Sensitivity (inc. biopsies)	0.96		Calculated
Specificity (inc. biopsies)	0.99		Calculated
Proportion of TPs requiring biopsy	0.24		Calculated
Proportion of TNs requiring biopsy	0.13		Calculated
Total serology costs	£15.52		Calculated
Disutility of FP diagnosis (unnecessary GFD)			
Change in social function score on SF-36	-8.300 (-15.800, -0.800)	Normal: μ=-8.30; σ=3.83	Kurppa et al. 2014
Coefficient for social function in mapping model	0.0011 (0.0007, 0.0015)	Normal: μ=1.1E-3; σ=2.0E-4	Ara & Brazier 2008
Disutility as absolute	-0.009		Calculated
Disutility as multiplier	0.989		Calculated

[a] *≥10 times the upper limit of normal*

G.1.4 Original cost–utility model – results

G.1.4.1 Relationship between diagnostic accuracy and model outputs

We found that the lifetime effectiveness of each strategy – in terms of QALYs accrued – was strongly correlated with the strategy's sensitivity. This is because false-negative diagnoses are associated with reduced QALYs (as a function of both persistent coeliac symptoms and increased likelihood of long-term complications, some of which may impact on life expectancy). Therefore, strategies with fewest false-negative diagnoses are those that accrue most QALYs. Conversely, the total costs of each strategy are strongly correlated with their specificity. This is predominantly because false-positive serological diagnoses incur additional costs due to unnecessary endoscopic biopsies that would be avoided with a more specific approach. These features were evident in the analyses for both adults (Figure 2) and children (Figure 3).

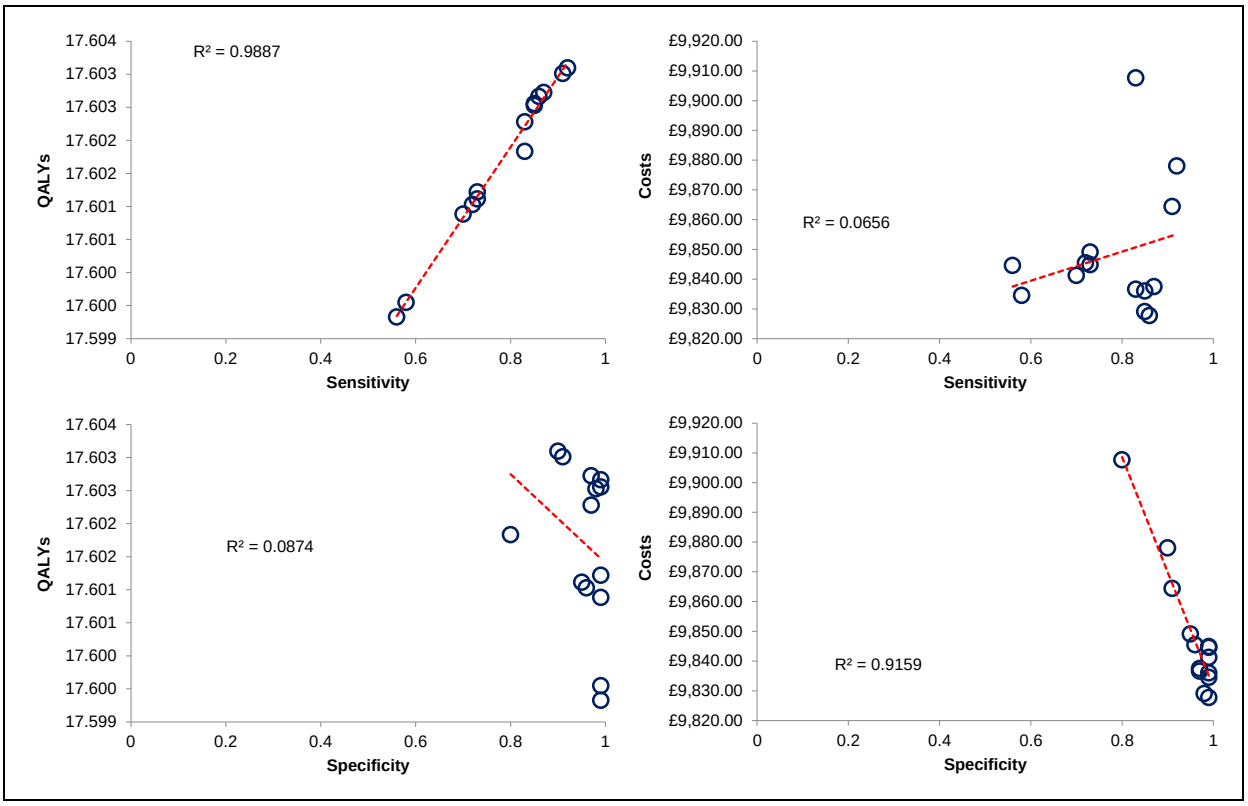


Figure 2: Relationship between diagnostic accuracy and modelled QALYs and costs (adults)

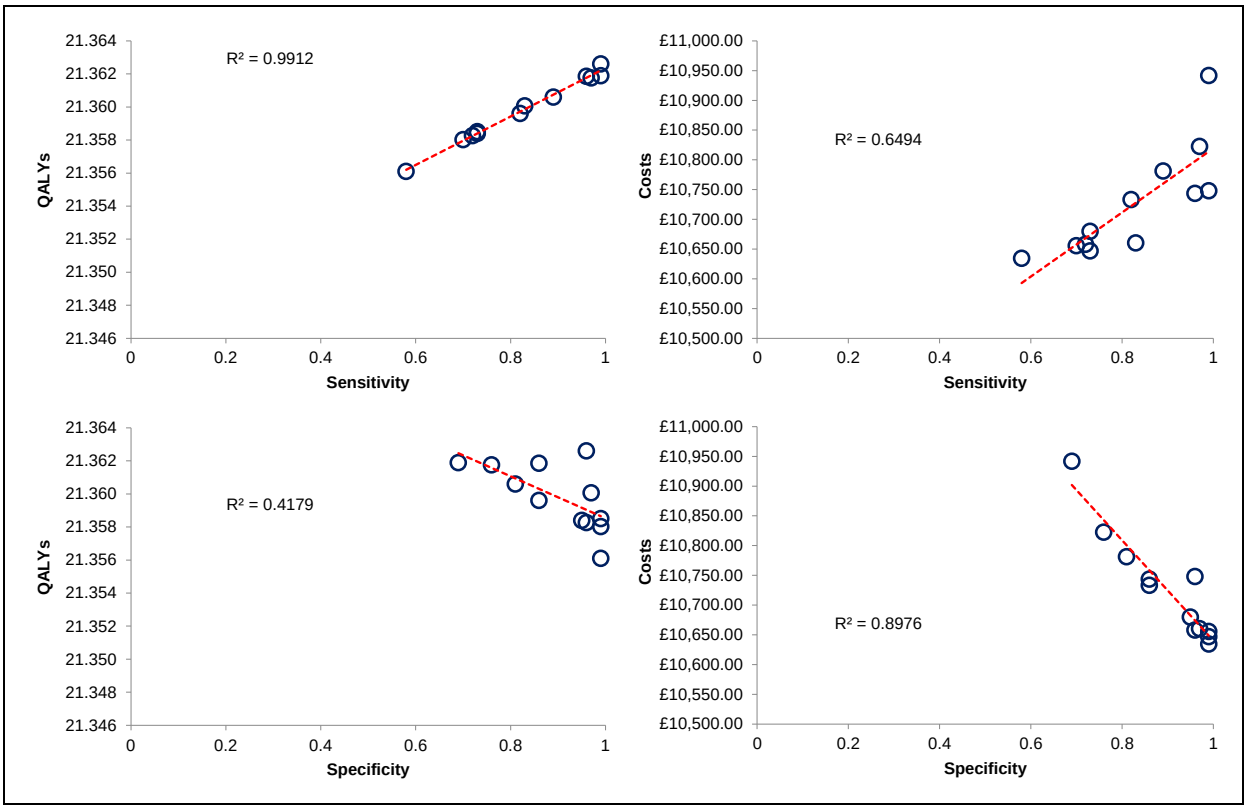


Figure 3: Relationship between diagnostic accuracy and modelled QALYs and costs (children)

Weighing these factors against each other leads to somewhat different conclusions in adults and children. In adults (Figure 4), greatest value for money (assessed as maximal net monetary benefit at £20,000 per QALY) tends to be achieved by strategies that are most sensitive (that is, those that minimise false-negative diagnoses and, therefore, maximise QALYs). In children (Figure 5), the approaches that demonstrate greatest value are those that have higher specificity (that is, those with fewest false-positive diagnoses that, therefore, minimise costs). The reason for this difference is that endoscopic biopsies are much more expensive in the paediatric population, as they are invariably performed under general anaesthesia. This finding was consistent with the GDG's view regarding the harms of false serology: the group believed it is appropriate to be more conservative in referring children for endoscopic biopsy because it is a much more significant undertaking for them than for adults. Therefore, a strategy with high specificity is a higher priority in children.

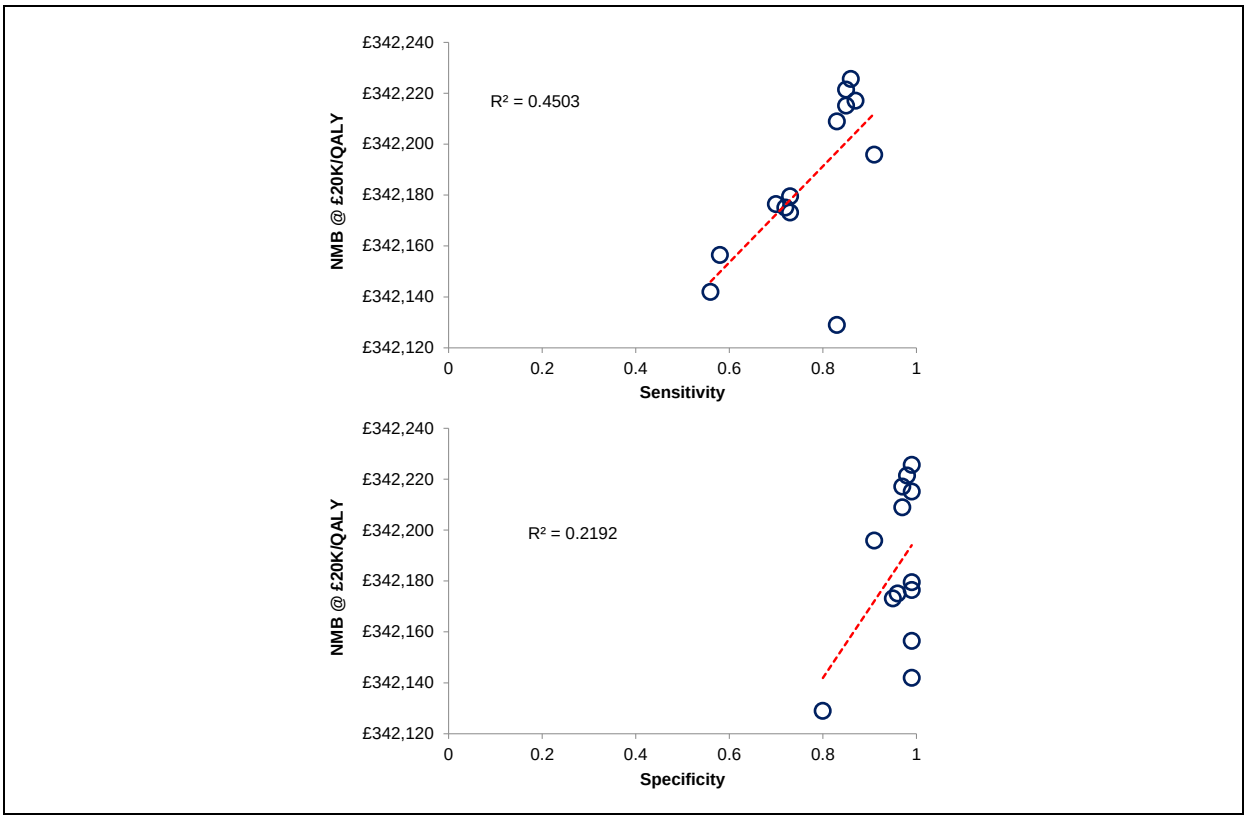


Figure 4: Relationship between diagnostic accuracy and cost effectiveness (adults)

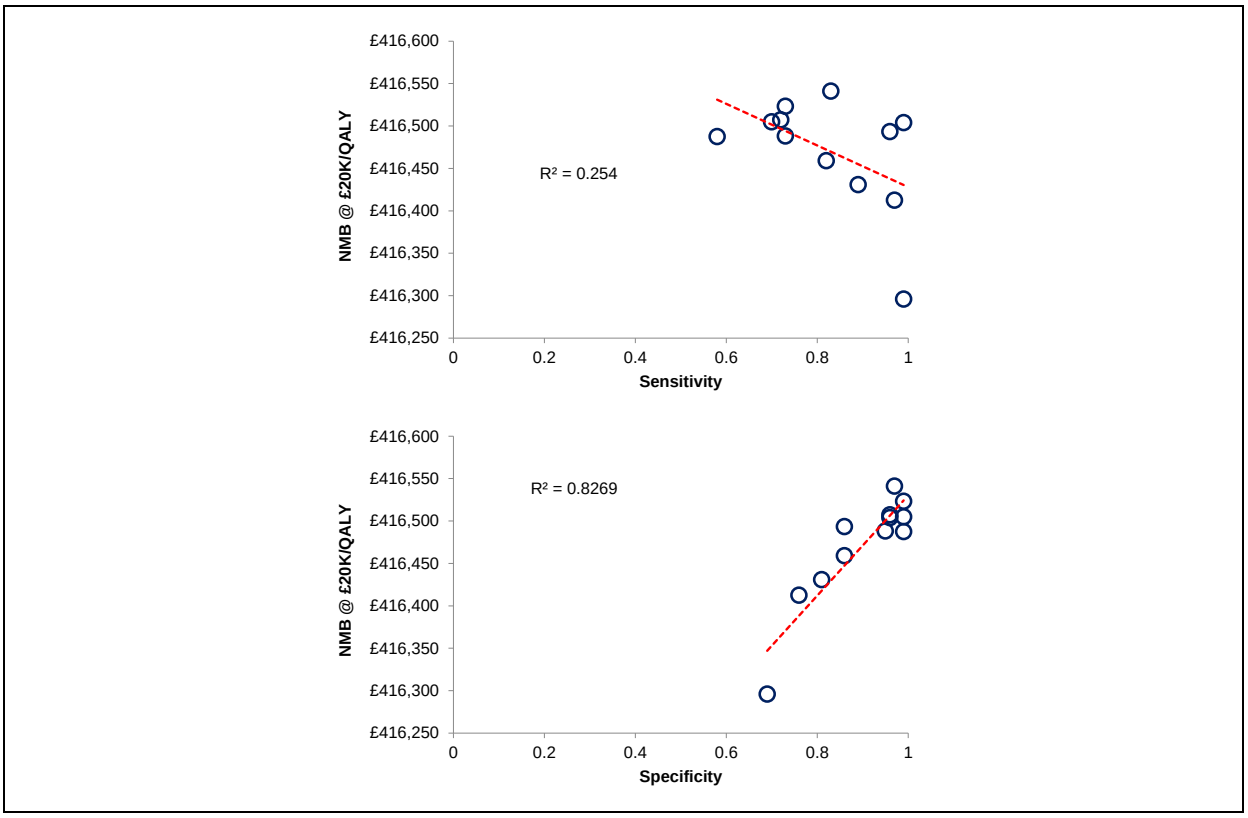


Figure 5: Relationship between diagnostic accuracy and cost effectiveness (children)

G.1.4.2 Base-case cost–utility results

Adults

Table 9 and Figure 6 show base-case cost–utility results.

In adults, the most effective strategy was the most sensitive – that is, considering people serologically positive if they are positive on either IgA tTG or IgA EMA. However, the incremental benefit of this approach came at a very high cost: the base-case ICER exceeded £170,000 per QALY. However, the model suggested that almost all the benefit of this approach could be achieved at lower cost by a strategy that tests IgA tTG in all people and reserves IgA EMA to classify cases in which IgA tTG results are weakly positive. Indeed, accounting for the costs of the tests themselves and the downstream consequences of true and false diagnoses over the lifetime of the cohort, the model estimated that this approach is associated with least net costs of all options.

Table 9: Base-case cost–utility results – adults

	Absolute		Incremental			Net Monetary Benefit	
Name	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)	£20K/QALY	£30K/QALY
StepIgATTG_equiv_then_IgAEMA	£9,831	17.6000				£342,170	£518,170
IgAEMA	£9,832	17.5999	£1	-0.0002	dominated	£342,166	£518,164
IgGDGP+IgADGP+IgAEMA	£9,838	17.5969	£7	-0.0032	dominated	£342,100	£518,069
BothIgATTG+IgAEMA	£9,839	17.5999	£8	-0.0001	dominated	£342,159	£518,158
IgGDGP	£9,840	17.5996	£9	-0.0004	dominated	£342,153	£518,149
StepIgATTG_then_IgAEMA	£9,841	17.6001	£10	0.0001	£98,399	£342,162	£518,163
IgGDGP+IgAEMA+IgATTG	£9,844	17.5982	£4	-0.0019	dominated	£342,120	£518,102
IgGDGP+IgATTG	£9,847	17.5984	£6	-0.0018	dominated	£342,120	£518,104
IgGDGP+IgADGP+IgAEMA+IgATTG	£9,848	17.5966	£7	-0.0035	dominated	£342,085	£518,051

Name	Absolute		Incremental			Net Monetary Benefit	
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)	£20K/QALY	£30K/QALY
IgGDGP+IgADGP+IgATTG	£9,848	17.5986	£7	-0.0016	dominated	£342,123	£518,109
IgGDGP+IgAEMA	£9,852	17.5985	£11	-0.0017	dominated	£342,117	£518,101
IgATTG	£9,867	17.6004	£27	0.0002	£113,994	£342,140	£518,144
EitherIgATTG+IgAEMA	£9,881	17.6004	£14	0.0001	£173,484	£342,128	£518,133
IgADGP	£9,910	17.5992	£30	-0.0012	dominated	£342,074	£518,066

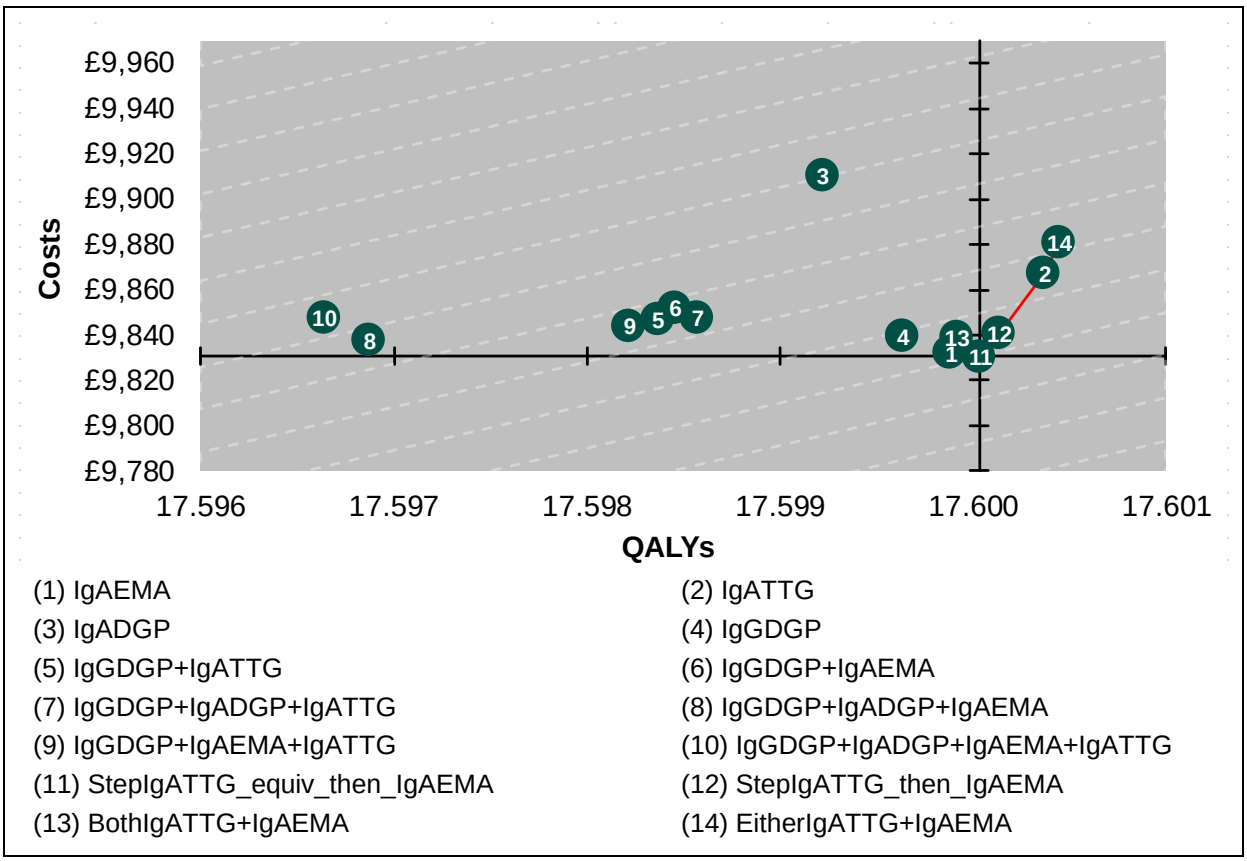


Figure 6: Base-case cost–utility results – cost–utility plane for adults

Children

In children (Table 10 and Figure 7), the most effective strategy was one that combined serological assays for IgA tTG and IgA EMA and HLA DQ2/DQ8 genotyping, an approach that had been shown to benefit from very high sensitivity and specificity in the clinical evidence review. However, because HLA genotyping is a relatively expensive test (over £70 each, some 5–8 times more expensive than any of the serological assays), its routine use is associated with significant costs, with the consequence that the 3-test strategy was associated with a relatively high ICER, around £33,800 per QALY gained compared with the next-cheapest non-dominated option.

The other strategies that appear attractive in children are combination approaches that include one or more DGP assay. It should be noted that all evidence for these tests in children came from a single study (Burgin Wolff et al., 2013).

Table 10: Base-case cost–utility results – children

Name	Absolute		Incremental			Net Monetary Benefit	
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)	£20K/QALY	£30K/QALY
IgGDGP+IgAEMA+IgATTG	£10,641	21.3756				£416,871	£630,628
IgGDGP+IgADGP+IgAEMA	£10,654	21.3781	£13	0.0025	£5,104	£416,909	£630,690
IgGDGP+IgADGP+IgAEMA+IgATTG	£10,663	21.3776	£9	-0.0005	dominated	£416,890	£630,667
IgGDGP+IgAEMA	£10,664	21.3779	£10	-0.0003	dominated	£416,893	£630,671
IgGDGP+IgATTG	£10,666	21.3797	£13	0.0015	£8,172	£416,927	£630,723
IgGDGP+IgADGP+IgATTG	£10,687	21.3780	£20	-0.0017	dominated	£416,873	£630,653
IgADGP	£10,741	21.3792	£75	-0.0004	dominated	£416,843	£630,636
IgATTG	£10,751	21.3815	£85	0.0019	ext. dom.	£416,879	£630,694
IgATTG+IgAEMA+HLA	£10,755	21.3823	£89	0.0026	£33,803	£416,891	£630,713
IgGDGP	£10,787	21.3802	£32	-0.0021	dominated	£416,817	£630,619
IgAEMA	£10,828	21.3814	£73	-0.0009	dominated	£416,801	£630,615
HLA	£10,950	21.3816	£195	-0.0007	dominated	£416,681	£630,497

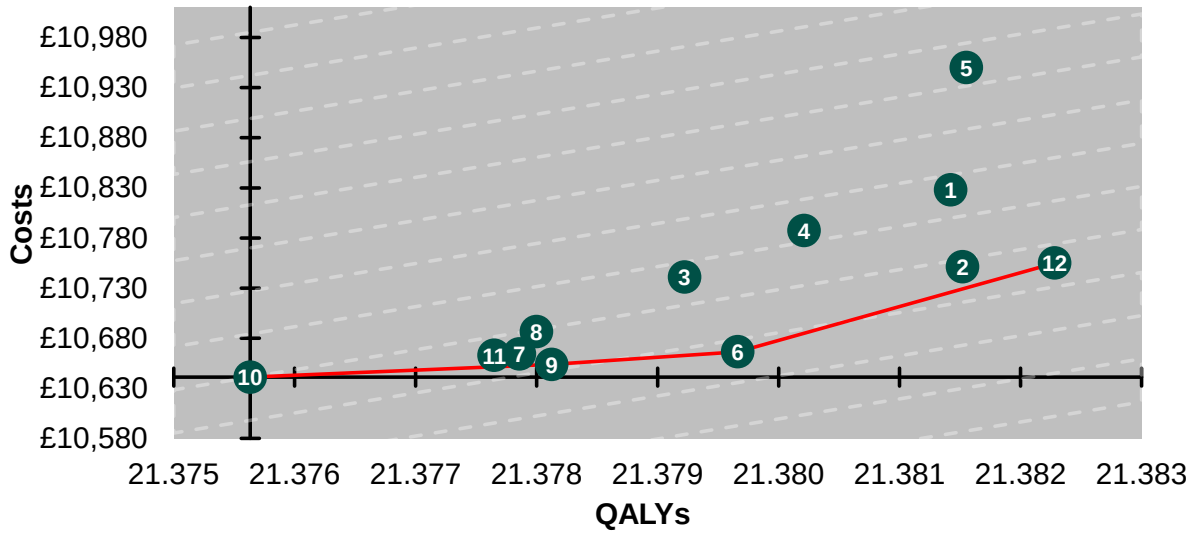


Figure 7: Base-case cost–utility results – cost–utility plane for children

G.1.4.3 Deterministic sensitivity analysis

Adults

Figure 8 shows the results of a one-way sensitivity analysis exploring the relationship between prevalence of coeliac disease in the population being tested and the value for money provided by each of the strategies.

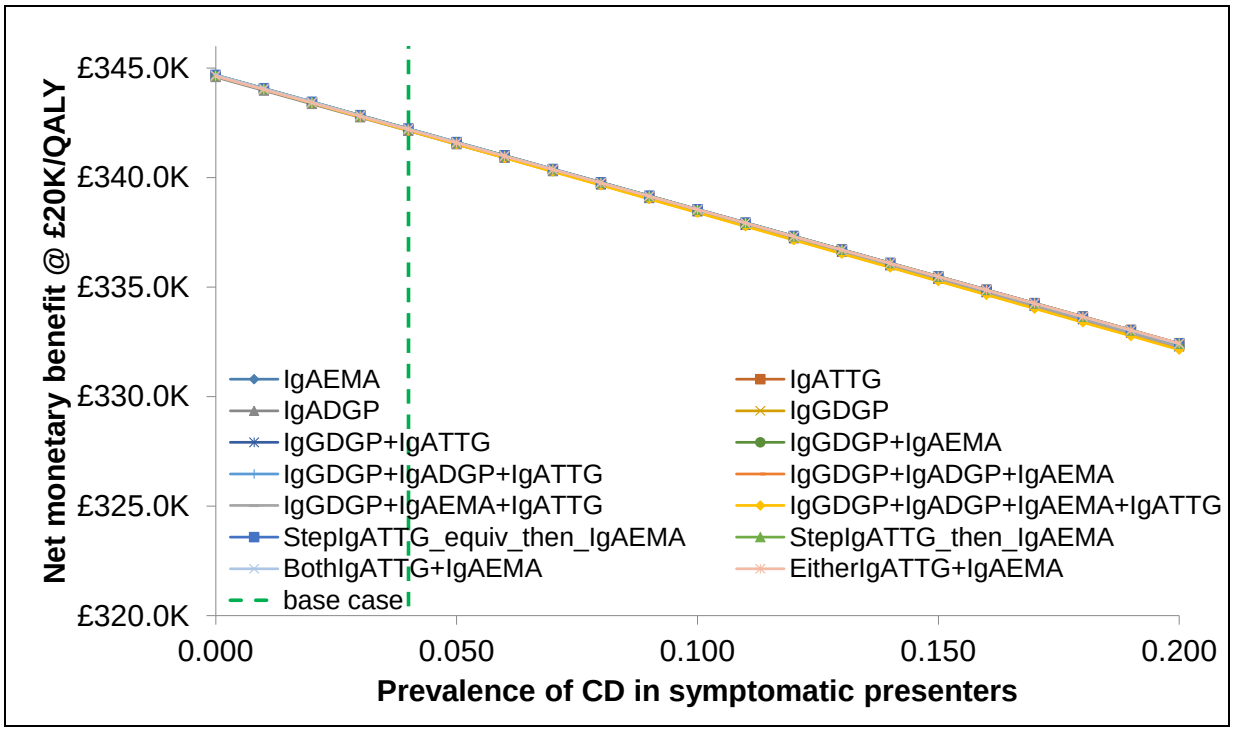


Figure 8: One-way sensitivity analysis – prevalence of coeliac disease (adults)

There is a very clear general trend for all simulated strategies to generate less health as prevalence increases. This is because people who have coeliac disease have lower quality of life than people who do not; therefore, a higher proportion of people with coeliac disease implies a lower overall quality of life for the cohort on average. A more important finding, which is rather less clear in the graph, is that, as prevalence rises, the incremental difference between strategies increases somewhat: the more likely any individual is to have coeliac disease, the greater value can be gained by the most accurate testing regimens. More particularly, specificity becomes less important as prevalence rises, and the marginal gains associated with small increments in sensitivity become increasingly valuable. If prevalence rises above 17.5%, a strategy consisting of IgA tTG assay alone becomes optimal and, if prevalence rises further to 27.5% or higher, best value is provided by an approach that offers both IgA tTG and IgA EMA and considers the person serologically positive if they are positive on either.

Figure 9 shows the results of a one-way sensitivity analysis exploring the additional capital costs that would be incurred, by some laboratories, in expanding their provision to enable them to undertake IgA tTG tests (see G.1.3.7).

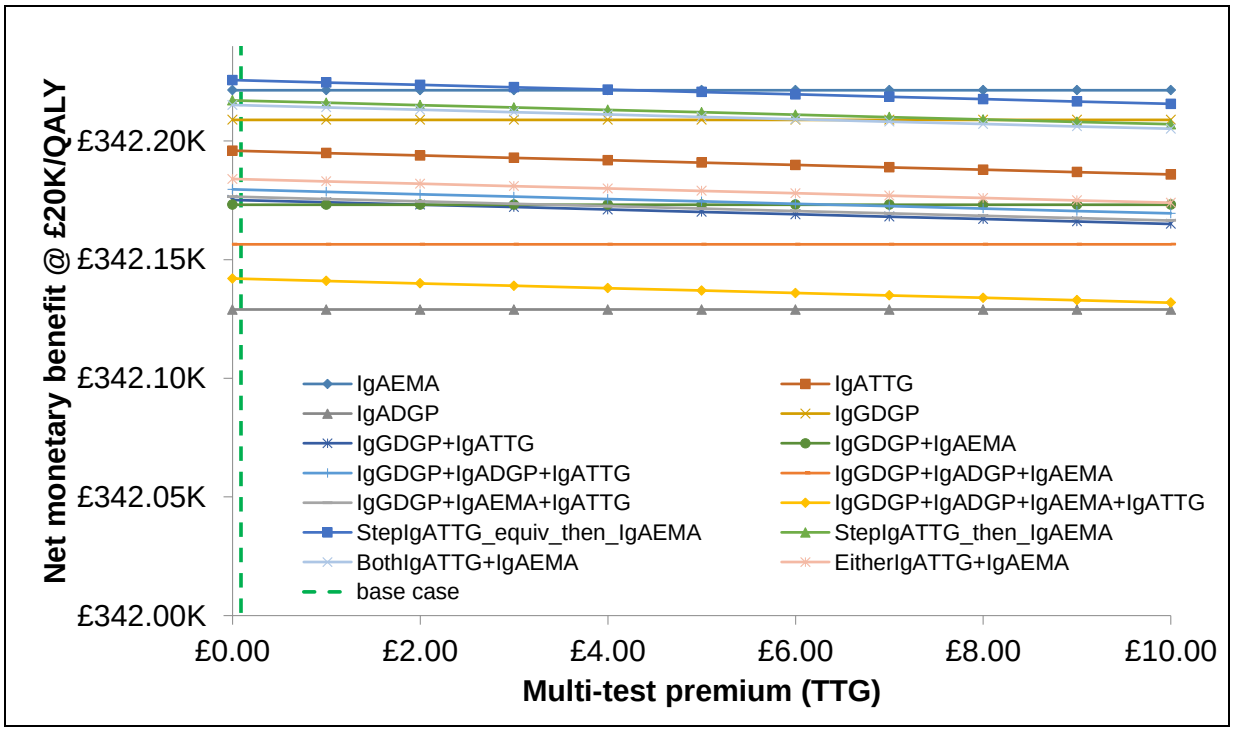


Figure 9: One-way sensitivity analysis – multi-test premium for strategies including IgA tTG (adults)

The total costs of increasing capacity would have to increase the unit-cost of every tTG test undertaken in England and Wales by over £4 per test (compared with a base-case estimate of 9p) before it would be preferable to rely on a single-test strategy. This is approximately equivalent to assuming that laboratories needing to purchase new equipment to undertake tTG assays would be asked to perform fewer than 350 tests for coeliac disease over the lifetime of the equipment, or that the equipment would cost £500,000 (compared to a best estimate of £12,000). None of these figures is within a plausible range; this gives support to the cost effectiveness of a testing strategy involving both IgA tTG and IgA EMA.

An analogous sensitivity analysis (not shown) demonstrated that the capital implications of increasing capacity for IgA EMA assay are not a determinant of overall cost effectiveness (largely because all of the best-value strategies include an IgA EMA component).

Probability of adherence to gluten-free diet had negligible impact on incremental cost-effectiveness results, when the parameter was varied over a broad range.

Children

Sensitivity analysis in children showed 2 circumstances under which it appears clearly cost effective to include routine HLA genotyping in the diagnostic algorithm: if the prevalence of coeliac disease in the population to be tested exceeds 8% (base case 4%; Figure 10) or if the annual probability of late detection coeliac disease – correcting false negative diagnoses – is 4.5% or lower (base case 13.2%; Figure 11).

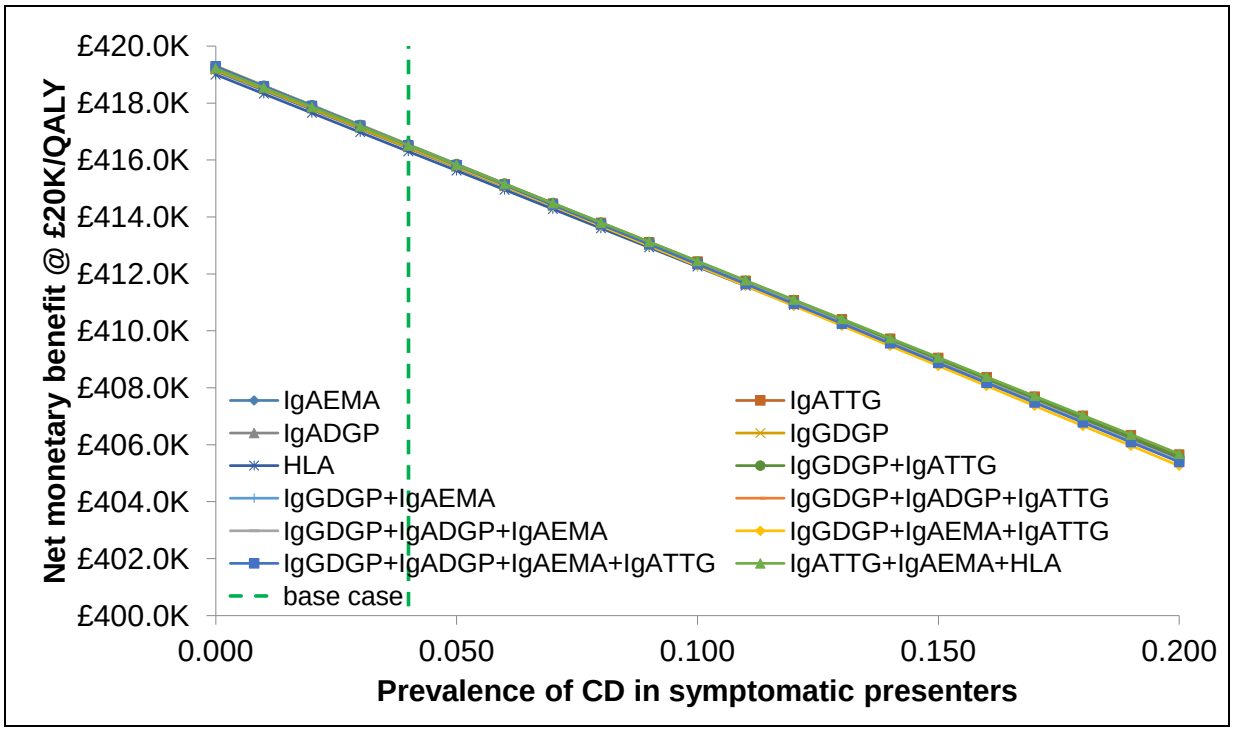


Figure 10: One-way sensitivity analysis – prevalence of coeliac disease (children)

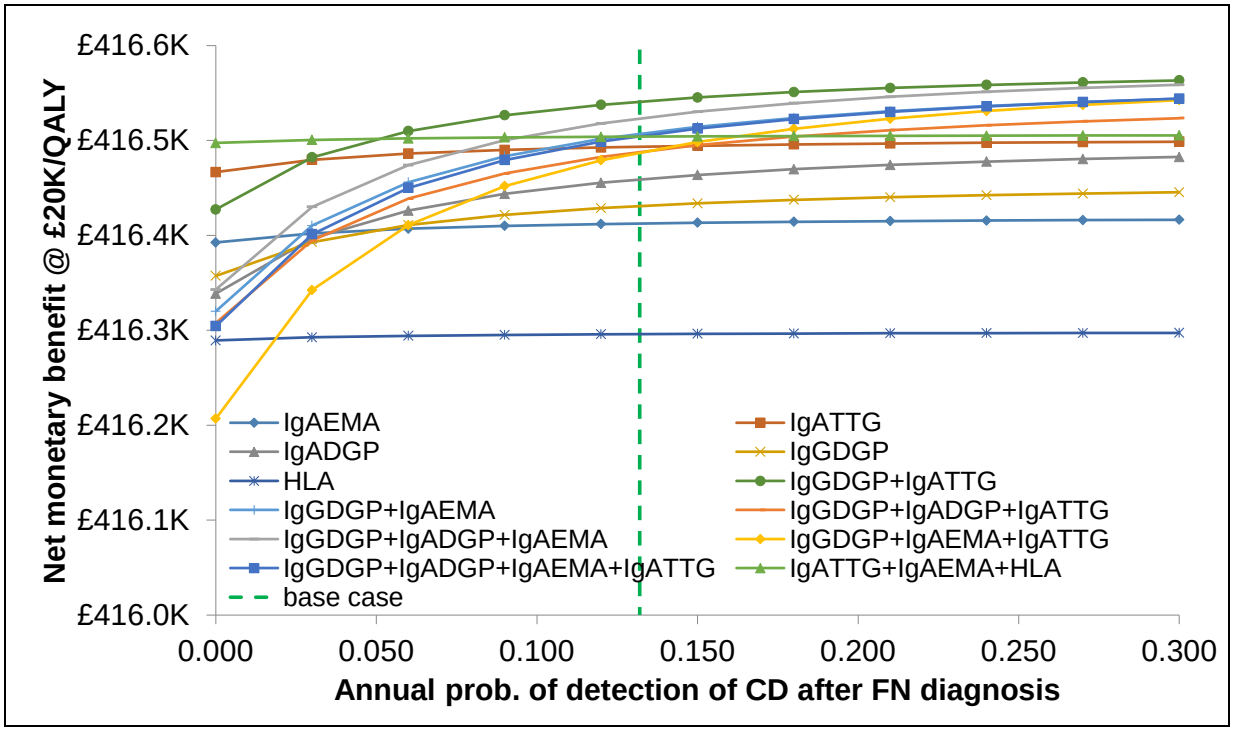


Figure 11: One-way sensitivity analysis – probability of late detection of coeliac disease (children)

Additional sensitivity analyses (not shown) demonstrated that the capital implications of increasing capacity for IgA tTG and/or IgA EMA assay are not a determinant of overall cost effectiveness within the broad range of possible costs explored. Probability of adherence to GFD was also not associated with significant changes in incremental differences between possible strategies.

G.1.4.4 Probabilistic sensitivity analysis

Adults

PSA reinforced the base-case findings: StepIgATTG_equiv_then_IgAEMA (that is, using IgA EMA only to categorise weakly positive IgA tTG findings) has the highest probability of providing best value for money (46.6% at a QALY value of £20,000; see Figure 12). As the assumed value of 1 QALY increases, the probability that it might be preferable to use IgA EMA to confirm all IgA tTG-positive cases rises; however, as the cost-effectiveness acceptability frontier (CEAF; Figure 13) shows, the expected value of this strategy is never optimal, regardless of the assumed cost-per-QALY threshold.

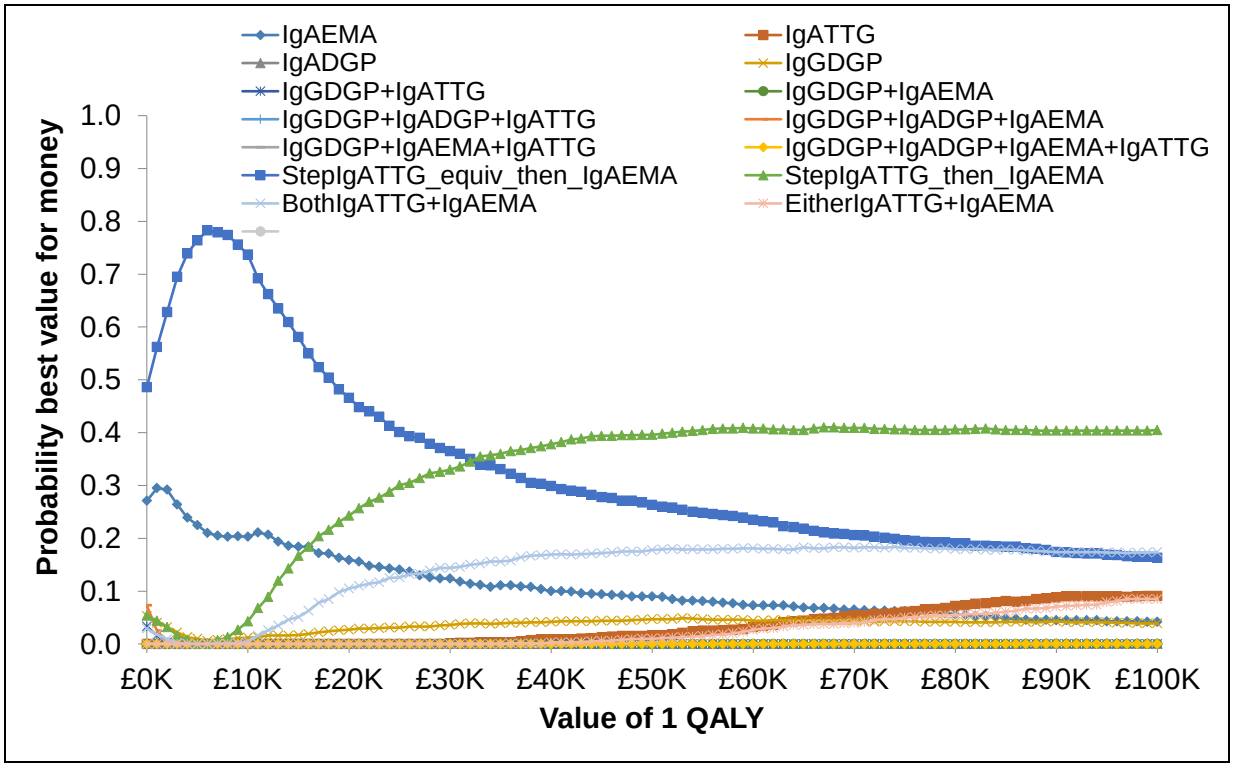


Figure 12: Cost-effectiveness acceptability curve (adults)

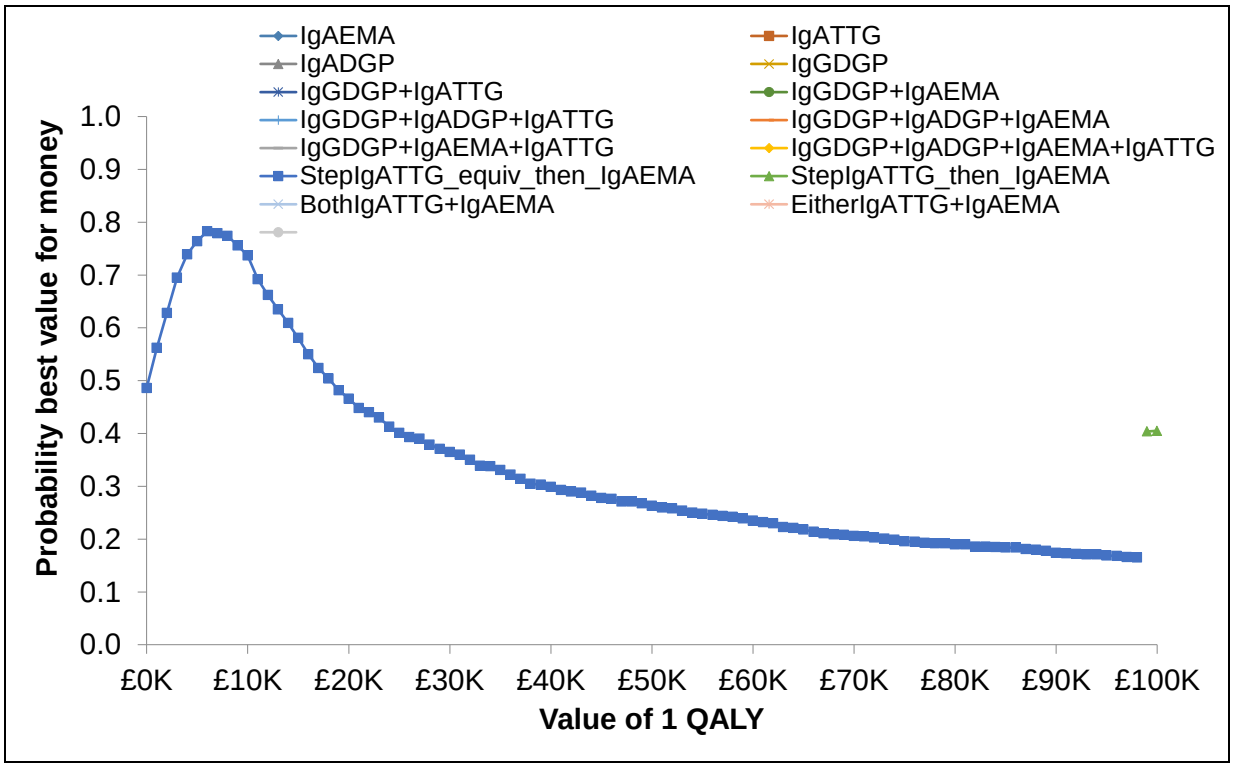


Figure 13: Cost-effectiveness acceptability frontier (adults)

Children

PSA shows that, at conventional cost-per-QALY thresholds and below, a DGP-containing strategy is likely to provide best value for money. As the assumed value of a QALY rises to £35,000 and higher, the optimal strategy becomes one that combines IgA tTG, IgA EMA and routine HLA genotyping. The CEAC is shown in Figure 14 and the CEAF is shown in Figure 15.

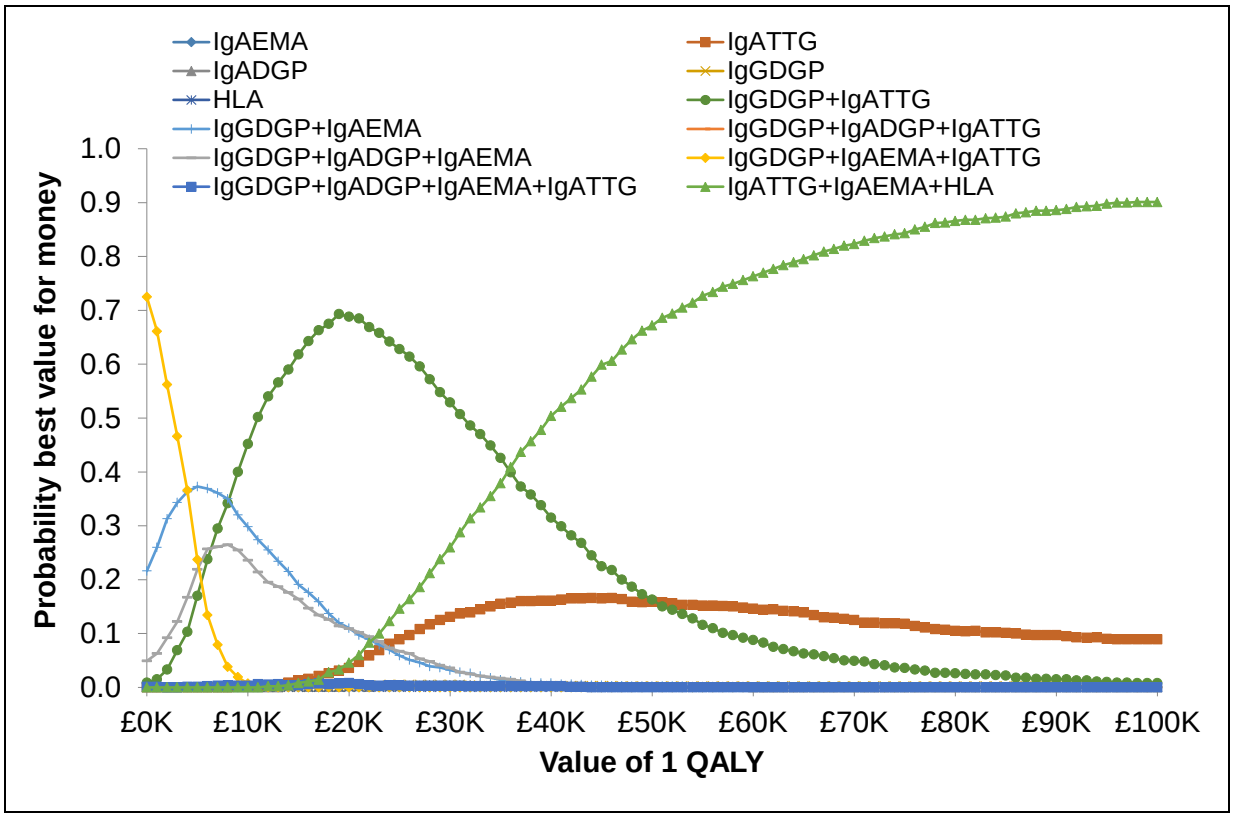


Figure 14: Cost-effectiveness acceptability curve (children)

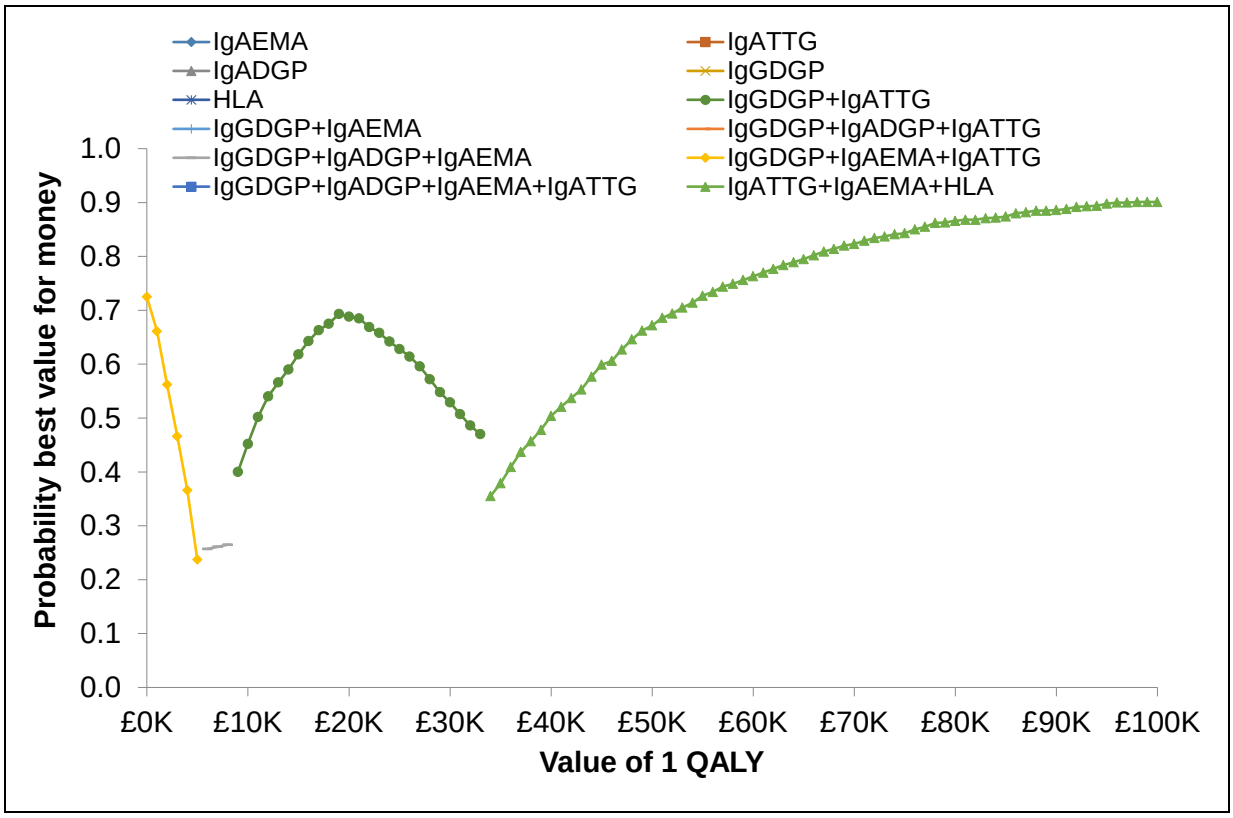


Figure 15: Cost-effectiveness acceptability frontier (children)

G.1.4.5 Scenario analysis – ESPGHAN criteria in children

In our scenario analysis approximating the ESPGHAN algorithm for diagnosing children suspected of coeliac disease (which has the important benefit of limiting endoscopic biopsies in children), this approach was extendedly dominated by IgGDGP+IgATTG and IgATTG+IgAEMA+HLA (see Table 11 and Figure 16).

The calculations suggested that, under the ESPGHAN algorithm, around 13.6% of children undergoing serological testing would still require biopsy. By comparison, when routine biopsy for all serologically positive people is assumed, all single tests result in higher biopsy rates, ranging from 16.7% for IgA DGP alone to 33.7% for HLA DQ2/DQ8 genotyping alone. Combinations of tests requiring children to be positive on all assays result in lower biopsy rates (3–8%), owing to their higher specificities.

Table 11: Scenario analysis – ESPGHAN criteria in children: cost–utility results

	Absolute		Incremental			Net Monetary Benefit	
Name	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)	£20K/QALY	£30K/QALY
IgGDGP+IgAEMA+IgATTG	£10,641	21.3756				£416,871	£630,628
IgGDGP+IgADGP+IgAEMA	£10,654	21.3781	£13	0.0025	£5,104	£416,909	£630,690
IgGDGP+IgADGP+IgAEMA+IgATTG	£10,663	21.3776	£9	-0.0005	dominated	£416,890	£630,667
IgGDGP+IgAEMA	£10,664	21.3779	£10	-0.0003	dominated	£416,893	£630,671
IgGDGP+IgATTG	£10,666	21.3797	£13	0.0015	£8,172	£416,927	£630,723
IgGDGP+IgADGP+IgATTG	£10,687	21.3780	£20	-0.0017	dominated	£416,873	£630,653
IgADGP	£10,741	21.3792	£75	-0.0004	dominated	£416,843	£630,636
ESPGHAN	£10,748	21.3810	£82	0.0014	ext. dom.	£416,872	£630,683
IgATTG	£10,751	21.3815	£85	0.0019	ext. dom.	£416,879	£630,694
IgATTG+IgAEMA+HLA	£10,755	21.3823	£89	0.0026	£33,803	£416,891	£630,713
IgGDGP	£10,787	21.3802	£32	-0.0021	dominated	£416,817	£630,619
IgAEMA	£10,828	21.3814	£73	-0.0009	dominated	£416,801	£630,615
HLA	£10,950	21.3816	£195	-0.0007	dominated	£416,681	£630,497

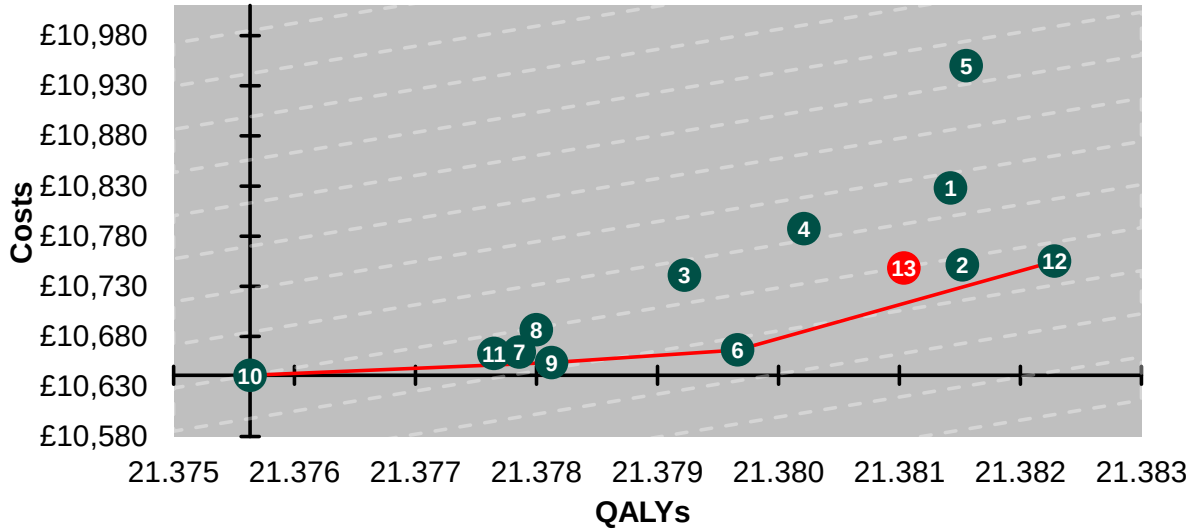


Figure 16: Scenario analysis – ESPGHAN criteria in children: cost–utility plane

In PSA, the approximated ESPGHAN algorithm was associated with a relatively low probability of providing optimal value for money (5.4% at a cost-per-QALY threshold of £20,000).

However, the strategy was, in broad terms, predicted to accrue similar health gains at similar cost to the other strategies simulated, here. It would be reasonable to argue that the margin of error inherent in approximating the algorithm in the absence of direct evidence is greater than the apparent difference between this approach and other simulated strategies.

G.1.5 Discussion

G.1.5.1 Principal findings

In adults, the most sensitive diagnostic strategies are likely to be the most cost-effective. This remains the case when the uncertainty in parameter estimates is taken into consideration through probabilistic sensitivity analysis.

The cost of diagnosing coeliac disease does not have a significant impact upon the lifetime costs accrued and therefore as the costs of the diagnostic tests remain reasonably similar, the choice of test need not been driven by its cost.

Of greater significance are the cost and quality of life implications of getting the diagnosis wrong. Of note, at the population level, a false-positive coeliac disease diagnosis, with the associated endoscopic procedure for biopsy is preferable to a false-negative diagnosis.

Accordingly, in adults, the most effective strategy was the most sensitive – that is, considering people serologically positive if they are positive on either IgA tTG or IgA EMA. However, the incremental benefit of this approach came at a very high cost: the base-case ICER exceeded £170,000 per QALY. However, the model suggested that almost all the

benefit of this approach could be achieved at lower cost by a strategy that tests IgA tTG in all people and reserves IgA EMA to classify cases in which IgA tTG results are weakly positive.

Although sensitivity was the main determinant of value in the adult population, small differences in sensitivity between strategies could be outweighed by larger differences in specificity. Although there were 2 strategies in the model that had higher sensitivity than IgA tTG with IgA EMA to determine weakly positive cases, the benefits associated with those strategies' superior true-positive rates were smaller than the harms and costs associated with their inferior false-positive rates (lower specificities).

In children, the specificity of the test takes greater prominence in its impact upon estimates of cost effectiveness. This is largely driven by the fact that a biopsy is more than double the cost in children as it is in adults. The most effective strategy was one that combined serological assays for IgA tTG and IgA EMA and HLA DQ2/DQ8 genotyping. However, its routine use is associated with significant costs, with the consequence that the 3-test strategy was associated with a relatively high ICER, around £34,000 per QALY gained compared with the next-cheapest non-dominated option.

The other strategies that appear attractive in children are combination approaches that include one or more DGP assay, which may be difficult to recommend in routine use. If DGP-containing strategies are excluded from the paediatric decision-space, the 3-test combination of IgA tTG, IgA EMA and HLA DQ2/DQ8 becomes the optimal approach, generating more QALYs than any of the individual tests alone, with ICERs lower than £5000 per QALY.

G.1.5.2 Strengths of the analysis

The model is based on all the available published evidence for coeliac disease diagnostic strategies and the evidence syntheses that could be produced from this evidence base.

In an attempt to represent the longer-term outcomes of treated and untreated coeliac disease the consequences of inaccuracy in the diagnostic strategies can be explored and used to inform decision making.

The potential long-term consequences of coeliac disease that are represented within the model are based on a clinical evidence base that was put together as part of this guideline update. This means the evidence is informed by a systematic review of published clinical data. The group of conditions represented by the model were prioritised and agreed with the GDG.

In updating the model structure used to support decision making in the original coeliac disease guideline, we were able to build on model structures that already had some face validity from the previous GDG's validation and the previous stakeholder consultation. With additional clinical evidence at our disposal, we were able to expand the detail of the downstream elements of the model to incorporate more specific risks which could also be dependent on a number of patient characteristics such as age and sex.

The model has face-validity through the iterative involvement of the GDG in the conceptualisation, parameterisation and validation of the model.

The functionality of the model was tested by a health economist within the team who had not been involved in its development. Validation checks involve both consideration of the model specification and its mechanics, including assessing formulae for accuracy and varying model inputs to check observed effects match expectations.

In building a model structure to represent a large proportion of the clinical pathway, we are able to adapt and build upon the structures to provide analysis for subsequent review questions.

G.1.5.3 Weaknesses of the analysis

The model assumes the decision to adhere to a gluten-free diet is made at the point of diagnosis and that this decision cannot be reversed within the timeframe modelled. There is also a clear distinction made between adherent and non-adherent, and this directly drives the risk of subsequent complications. However gluten-free diet adherence may in some individuals be cyclical with periods of strict adherence and times of lapsing adherence. It may also be that interventions provided by the health service such as dietary education, may alter an individual's tendency to adhere, some years after the initial coeliac disease diagnosis. The reverse too could be the case, where a life-event for example results in a previously adherent individual no longer complies with their gluten-free diet.

The diagnostic test options are limited to those in which there was evidence within a population with suspected symptoms of coeliac disease. Where specific evidence is available for adult or child populations, this evidence was used to estimate the accuracy of the diagnostic test. When only evidence within a mixed population of adults and children is available this evidence is used for both the adult and child populations. However where evidence is only available for one of the sub-groups, this results in the test being unavailable in the other groups, therefore the choices of diagnostic tests and testing strategies considered for adults and children may differ.

There was insufficient evidence to generate a meta-analysed estimate of the sensitivity and specificity of each test, in both adult and child populations. This results in some estimates of accuracy being based on the evidence of one study alone.

Our assumption that biopsy is 100% accurate is an acknowledged simplification of a more complex reality. However, it was one that the GDG were happy to agree. Although they recognised that, in reality, biopsy will not always provide perfect results, it is not possible to specify a pathway with a 'better' reference standard, as no such thing exists and, in practice, people are treated on the basis of their biopsy results. Of course, studies in people with coeliac disease are subject to the same problem (that is, they are contaminated with a very small proportion of people who would be classified as false positives according to a truly perfect reference standard). Therefore, it would not be appropriate to adjust for this fact in our use of this evidence. We do include an estimate of the costs associated with repeat biopsies due to unreadable results.

In clinical practice it may be that patients presenting with the long-term complications we are representing within the model is the factor that instigates an investigation for coeliac disease rather than a presentation due to coeliac-type symptoms or other risk factors. The way the epidemiology is represented within the model with the presence of disease elevating the probability of developing the complications; however means that a diagnosis for an alternative presentation is not taken into consideration.

G.1.5.4 Conclusions

The diagnostic strategies that are the most cost effective differ in the adult and child populations.

In adults, the main driver of cost-effectiveness is test strategy sensitivity. The penalty, at a population level, in terms of missing people with true coeliac disease is much higher than that of exposing some people to an unnecessary biopsy.

In children, the specificity of the testing strategies takes greater prominence, largely due to the increased cost of performing biopsies in children.

G.2 Active case-finding in populations at increased risk of coeliac disease (full guideline section 4.4)

G.2.1.1 Decision problem

Table 12: Research questions

RQ2	Should active case-finding be implemented in people with coexisting conditions/subgroups that are associated with an increased risk of coeliac disease?

Table 13: PICO

Population	Patients with coexisting conditions/subgroups that are associated with an increased risk of coeliac disease, without symptoms that would lead them to seek investigation
Intervention	Screening for coeliac disease
Comparator	No screening
Outcomes	Cost–utility analysis based on the quality of life (in quality adjusted life years[QALYs]) and costs of correctly diagnosing and failing to diagnose coeliac disease.

G.2.2 Systematic review of published cost–utility analyses

G.2.2.1 Methods

Inclusion and exclusion criteria

The economic literature review aimed to identify economic evaluations in the form of cost–utility analyses exploring the costs and effects of screening for coeliac disease in different at-risk groups.

Search strategy

The search strategy was based on that used to identify clinical evidence for this question, with the RCT filter removed and a standard economic filter applied (see appendix C).

G.2.2.2 Results

Study identification

The search returned 236 studies; after title and abstract screening, we ordered the full texts of 20 studies. On perusal of the retrieved papers, 4 cost–utility analyses were found of relevance to the question.

Included studies

Mein & Ladabaum (2004) and Mohseninejad et al. (2013) explored testing people with irritable bowel syndrome (IBS) for coeliac disease, Swigonski et al. (2006) looked at case-finding in children with Down syndrome, and Dretzke et al. (2004) analysed children newly diagnosed with type 1 diabetes.

Table 14 provides details of the design, quality and results of included studies.

1 **Table 14: Economic evidence profiles for included cost–utility analyses**

Study, setting, quality	Data sources	Other comments	Incremental (screening v. no screening)			Conclusions	Uncertainty
			Cost (£)	Effect (QALYs)	ICER (£/QALY)		
Irritable bowel syndrome							
Mein & Ladabaum (2004) USA **Partially applicable**[a,b,c] **Potentially serious limitations**[d,e]	**Effects:** Diagnostic accuracy estimates taken from published sources **Costs**: Medicare reimbursement data, study site institution costs and published sources (US $). Cost data year 2003. **Utilities:** Published sources.	No screening compared to 2 strategies: TTG only & Antibody panel (TTG, IgA AGA, IgG AGA & IgA deficiency test).	TTG only vs no screening: $130 Antibody panel vs no screening:$254	TTG only vs no screening: 0.0177 Antibody panel vs no screening: 0.0181	TTG only vs no screening: $7,400 Antibody panel vs no screening:$14,000	Serological testing to diagnose coeliac disease in patients with symptoms that would be consistent with a diagnosis of IBS is cost-effective. These results are likely to hold even with a reduction in coeliac prevalence and the utility gains associated with treated coeliac disease.	Threshold = <$50,000 per QALY TTG only vs no screening: 98%

Study, setting, quality	Data sources	Other comments	Incremental (screening v. no screening)			Conclusions	Uncertainty
			Cost (£)	Effect (QALYs)	ICER (£/QALY)		
Mohseninejad et al. (2013) Netherlands **Partially applicable**[f,g] **Potentially serious limitations**[h]	**Effects:** Diagnostic accuracy figures taken Dutch coeliac disease and dermatitis herpetiformis guidelines. **Costs:** Dutch CD guidelines, the Dutch Coeliac Disease organisation and published sources (€). Cost data year 2009. **Utilities:** EQ-5D values from published sources	CD diagnosis is assumed to take place after a 4-year delay (this is varied in sensitivity analysis). A CD diagnosis replaces an IBS diagnosis within the model; therefore CD & IBS do not exist concurrently in patients.	€418	0.067	Reported as approx. €6,200 [Calculated ICER: €6,238.81]	Testing IBS patients with diarrhoea or mixed symptoms for coeliac disease is likely to be cost-effective. Excluding patients who only experience constipation IBS symptoms improves the cost-effectiveness of testing. Health gains from CD diagnosis and time remaining undiagnosed are important factors; however the results remain reasonably robust.	At thresholds greater than €15,000/QALY the probability that screening is cost-effective reaches 1.

Study, setting, quality	Data sources	Other comments	Incremental (screening v. no screening)			Conclusions	Uncertainty
			Cost (£)	Effect (QALYs)	ICER (£/QALY)		
Children with newly diagnosed type 1 diabetes							
Dretzke et al (2004) UK NHS perspective **Partially applicable**[i] **Potentially serious limitations**[j,k]	**Effects:** systematic review of diagnostic accuracy data. **Costs:** Various published sources including Cost data year 2004 **Utilities:** Estimated by authors		Not reported	Not reported	EMA: £12,250 TTG: £12,970	EMA + confirmatory biopsy vs no screening was the most cost-effective option.	No PSA A small utility decrement for being on a GFD results in lower ICERs for each of the screening strategies. Other parameters influential to the cost-effectiveness estimates include the cost of a GFD, the utility differences between health states, the coeliac-associated reduction to life expectancy and the late detection rate.
Children with Down syndrome							
Swigonski et al. (2006) US children's hospital **Partially applicable**[a,l,m]	**Effects:** Diagnostic accuracy figures taken from a systematic review. **Costs:** Published sources (US $). Cost data year 2005. **Utilities:**	Model is limited to the potential benefits of preventing lymphoma	$1,448.20	-0.00241	Dominated	Screening for coeliac disease in asymptomatic patients does not improve quality of life and is more costly than a strategy without screening.	Not reported

Study, setting, quality	Data sources	Other comments	Incremental (screening v. no screening)			Conclusions	Uncertainty
			Cost (£)	Effect (QALYs)	ICER (£/QALY)		
Potentially serious limitations[k,n]	Published sources (some are SF-36 converted to EQ-5D)						

[a] *US healthcare system*
[b] *3% discount rate*
[c] *Quality of life is measured through symptomatic improvement only. Any potential impact of a CD diagnosis on life expectancy is excluded.*
[d] *No long-term health impacts modelled*
[e] *Costs of GFD not included*
[f] *Dutch healthcare system*
[g] *Discounts rates of 1.5% for health benefits and 4% for costs*
[h] *CD utility from UK EQ-5D data; however the study required the patients to recall their quality of life before diagnosis and is therefore susceptible to significant recall bias*
[i] *Discounts rates of 1.5% for health benefits and 6% for costs*
[j] *Utility values are estimated by authors*
[k] *No probabilistic sensitivity analysis*
[l] *GFD costs from patient perspective*
[m] *No discounting applied*
[n] *No long-term complications other than lymphoma considered*

G.2.2.3 Discussion

As the studies in the systematic review were largely conducted in health settings outside of the UK and addressed long-term complications differently in each case, comparisons across disease areas were problematic. The GDG identified that this was a high-priority area for original health economic analysis and therefore to supplement the evidence from the systematic review a de novo health economic analysis was produced.

G.2.3 Original cost–utility model – methods

G.2.3.1 Overview of the model

Table 15: Modelled population(s) and intervention(s)

Populations	Adults and children with an increased risk of coeliac disease: • First-degree relatives of people with coeliac disease • People with type 1 diabetes • People with autoimmune thyroid disease • People with irritable bowel syndrome
Intervention	CD screening
Comparator	No screening
Outcomes	Cost–utility analysis based on the benefits and harms (estimated in quality-adjusted life years[QALYs]) and costs of diagnosing coeliac disease.

We asked the GDG to prioritise the key subgroups of interest to be assessed within the economic model. They chose first-degree relatives, type 1 diabetes, autoimmune thyroid disease and irritable bowel syndrome.

The economic model for this question is based on the one used for the diagnostic question in people with symptoms of coeliac disease. Details of model structure and common parameters are provided in section G.1.3, above.

The major modification necessary to model this question was the introduction of additional strata allowing the differentiation between subclinical and symptomatic coeliac disease.

It was also necessary to introduce an additional arm simulating no testing, with which serological strategies could be compared, in order to estimate the value that can be expected from active case-finding. This was simply implemented as an additional diagnostic strategy with sensitivity of 0 (that is, 100% false-negative rate), specificity of 1 (that is, no false positives) and no test costs.

G.2.3.2 Additional assumptions

The assumptions of the underlying model apply here (with the exception of the assumed population); see Table 4. Modifying the model to explore case-finding requires some additional assumptions:

- The risk of long-term complications is independent of the coexisting condition and is entirely related to the presence of coeliac disease and whether or not it is treated.
- All conditions occur concurrently with coeliac disease (that is, coeliac disease is not a differential diagnosis for people who have been erroneously diagnosed with the condition in question). Therefore, in the absence of quality of life data in populations of individuals with both conditions, we use a quality of life value for the coexisting condition as a

multiplier to the underlying health state which is driven by the presence of coeliac disease and associated symptoms.

G.2.3.3 Additional parameters – all populations

To adapt the model to represent this decision problem, it was necessary to adopt a number of additional or alternative parameters.

See section G.1.3.2 for details of our general approach to identifying and selecting model parameters.

Quality of life – subclinical coeliac disease

In contrast to the model for symptomatic diagnosis, the case-finding model assumed that the populations of interest did not experience symptoms sufficient to trigger CD testing in routine practice. Therefore, we required alternative estimates of quality of life for people with 'subclinical' coeliac disease.

We revisited the studies identified in our systematic review of publications reporting quality of life of people with coeliac disease using EQ-5D or SF-36 (see G.1.3.8).

The evidence used in the model's base case was drawn from an Argentinian study in which quality of life was measured (using the SF-36) at the point of diagnosis and following 3 months' treatment with a GFD (Nachman et al. 2009). This suggested that people with subclinical coeliac disease who adopt a GFD experience quality of life that is, on average, approximately 1.5% better than those who continue to ingest gluten. The authors report that differences in individual SF-36 domain scores were not significant (although there was a trend towards improvement in the pain dimension). The study appears to have been well conducted; however, the parameter of interest is drawn from a small subgroup of just 8 people with subclinical CD. As a result, the estimates of effect are very uncertain. However, this uncertainty is propagated through our model: although our base-case parameters give a small HRQoL advantage to people with subclinical coeliac disease who adopt a GFD, the relevant values are associated with appropriately wide confidence intervals, so, in Monte-Carlo sampling for PSA, the utility values for people who do and do not follow a GFD will vary widely and reverse order frequently. This is an appropriate reflection of data that are consistent with a HRQoL advantage, no advantage or a disadvantage for people with subclinical coeliac disease commencing a GFD.

Probability subclinical coeliac disease becomes symptomatic

In the absence of case-finding, a proportion of people with subclinical coeliac disease would eventually receive a correct diagnosis. The model assumes this is a 2-stage process: people with subclinical disease have a probability of developing symptoms, and people with symptomatic coeliac disease have a probability of diagnosis. The latter transition is already parameterised in the model – it is used to estimate the probability of late detection of disease in false-negative cases. The development of symptoms requires additional parameters.

There is an absence of evidence directly addressing this issue: by definition, people with occult disease cannot be followed up as a cohort. Therefore, to approximate the necessary transitions, we relied on evidence about the age-specific prevalence of diagnosed coeliac disease. Because the prevalence of diagnosed disease rises as people get older, we can assume that (if incidental diagnosis is negligible) the rate of increase in prevalence approximates the rate at which people begin to develop symptoms. This can then be compared against the seroprevalence of coeliac disease in samples of the population to estimate the likelihood of disease ever becoming clinically overt.

The values used and rates estimated in this way are given in Table 16.

Gluten-free diet adherence – screen-detected children

Specific information was available on the probability that children who receive a diagnosis of coeliac disease via screening (that is, children whose disease was subclinical at the point of diagnosis), so we used this in the model. See Table 16.

G.2.3.4 Additional parameters – condition-specific

For each modelled population, we required a number of condition-specific parameters:

- **Prevalence of coeliac disease.** We drew these values from the evidence synthesis conducted as part of the clinical review identifying populations at an increased risk of developing coeliac disease (see main guideline, section 4.2). The GDG asked us to use UK-specific data only, where it was available; if no UK-only studies were available for the population in question, we used the pooled value for all included studies.
- **Quality of life associated with the condition/characteristic.** The baseline utility value for people in the population of interest, to which multipliers reflecting experience of coeliac disease and long-term complications are then applied.
- **Life expectancy of people with the condition/characteristic.** It is important to account for the projected life expectancy of people who might be candidates for case-finding. This is especially true because a proportion of the benefit that might be expected from true-positive diagnosis of coeliac disease is in reducing the likelihood of long-term complications; therefore, any significant reduction in life expectancy would attenuate the potential for this benefit to be realised.

All these parameters are detailed in Table 16.

We did not include any costs associated with the diagnosis or treatment of the coexisting condition, as we considered these to be unrelated to the question of interest, and essentially invariant to better or worse diagnosis of coeliac disease.

We did not identify any evidence that allowed us to adopt condition-specific test accuracy data. Therefore, we assumed that the sensitivity and specificity of the tests was invariant to the underlying population, and we used data from the review of diagnostic accuracy in people presenting with symptoms suggestive of coeliac disease (see G.1.3.4).

30 **Table 16: Additional and alternative parameters required for case-finding model**

Parameter	Value (95%CI)	Distribution and parameters	Source
Prevalence			
Ln[odds] of CD in modelled populations:			
First-degree relatives	-2.42 (-3.04, -1.79)	Normal: μ=-2.42; σ=0.32	Pooled value from clinical review (see full guideline, section 4.2)
Type 1 diabetes	-3.38 (-3.72, -3.03)	Normal: μ=-3.38; σ=0.18	UK-specific value from clinical review (see full guideline, section 4.2)
Autoimmune thyroid disease	-3.71 (-4.19, -3.23)	Normal: μ=-3.71; σ=0.25	Pooled value from clinical review (see full guideline, section 4.2)
Irritable bowel syndrome	-3.10 (-3.57, -2.63)	Normal: μ=-3.10; σ=0.24	UK-specific value from clinical review (see full guideline, section 4.2)
Prevalence of CD in modelled populations:			
First-degree relatives	8.2%		Calculated
Type 1 diabetes	3.3%		Calculated
Autoimmune thyroid disease	2.4%		Calculated
Irritable bowel syndrome	4.3%		Calculated
Adherence to GFD			
Probability of adhering to GFD (screen-detected children)	0.710 (0.580, 0.843)	Beta: α=31; β=12	Kinos et al. 2012
Probability subclinical CD becomes symptomatic			
Prevalence of diagnosed CD in general population			
5-17	0.1% (0.1%, 0.1%)	Normal: μ=1.3E-3; σ=4.3E-5	West et al. 2014
18-29	0.2% (0.1%, 0.2%)	Normal: μ=1.5E-3; σ=4.7E-5	
30-49	0.2% (0.2%, 0.2%)	Normal: μ=2.3E-3; σ=4.2E-5	
50-69	0.4% (0.4%, 0.4%)	Normal: μ=3.7E-3; σ=5.9E-5	
70+	0.4% (0.4%, 0.4%)	Normal: μ=3.8E-3; σ=8.6E-5	
Seroprevalence of CD in general population (age >65)	0.8% (0.5%, 1.2%)	Normal: μ=8.4E-3; σ=1.9E-3	West et al. 2003

Parameter	Value (95%CI)	Distribution and parameters	Source
Annual probability symptoms develop			
0-4	0.033		Calculated
5-17	0.002		Calculated
18-29	0.010		Calculated
30-49	0.013		Calculated
50-69	0.001		Calculated
70+	0		Assumption
Utilities			
All screen-detected cases			
Healthy controls	0.904 (0.799, 0.973)	Beta: α=37.42; β=3.97	Nachman et al. 2009
Subclinical CD no GFD	0.816 (0.730, 0.889)	Beta: α=72.75; β=16.39	
Subclinical CD on GFD	0.828 (0.740, 0.901)	Beta: α=67.90; β=14.09	
Impact of GFD on subclinical CD	1.015		Calculated
Decrement for subclinical CD (no GFD)	0.903		Calculated
Decrement for subclinical CD (on GFD)	0.916		Calculated
Coexisting conditions			
Type 1 diabetes			
People with T1D	0.830 (0.788, 0.868)	Beta: α=280.35; β=57.42	Solli et al. 2010
Age- & sex-matched general population	0.845		Calculated
Proportional decrement	0.982		Calculated
Autoimmune thyroid			
People with blood and immunity disorders	0.728 (0.691, 0.763)	Beta: α=426.56; β=159.37	HEDS
People without blood and immunity disorders	0.833 (0.812, 0.853)	Beta: α=1058.41; β=212.19	
Proportional decrement	0.874		Calculated
IBS			
People with IBS	0.675 (0.635, 0.714)	Beta: α=359.67; β=173.18	HEDS

Parameter	Value (95%CI)	Distribution and parameters	Source
Controls	0.810 (0.775, 0.843)	Beta: α=416.05; β=97.59	
Proportional decrement	0.833		Calculated

G.2.4 Original cost–utility model – results

G.2.4.1 First-degree relatives of people with coeliac disease – adults

Base-case cost–utility results

Base-case incremental cost–utility results are tabulated in Table 17 and depicted on the cost–utility plane in Figure 17.

As the cost–utility plane very clearly illustrates, all testing strategies result in improved quality of life at increased cost compared with no testing. The choice of optimal serological strategy closely mirrors that in the symptomatic diagnosis question (see G.1.4.2). The most sensitive strategies (IgA tTG alone and EitherIgATTG+IgAEMA [that is, considering people serologically positive if they are positive on either IgA tTG or IgA EMA]) produce greatest health gains, but the incremental benefits are small and come at substantial incremental cost, when compared with the recommended strategy in symptomatic people (that is, one that tests IgA tTG in all people and reserves IgA EMA to classify cases in which IgA tTG results are weakly positive). This approach has an ICER of £14,000 per QALY gained compared with no testing.

Deterministic sensitivity analyses

One-way sensitivity analyses exploring the model's sensitivity to key parameters are illustrated below.

Case-finding can be assumed to produce health at a cost of less than £20,000 per QALY if the prevalence of coeliac disease in the tested population exceeds 2%; this is substantially lower than the base-case estimate of 6.8% (Figure 18).

The ICER remains below £20,000 as long as it can be assumed that a gluten-free diet improves the health-related quality of life of people with subclinical coeliac disease by 1.2% or more (base-case 1.48%; Figure 19).

Probabilistic sensitivity analysis

The results of probabilistic sensitivity analysis are shown in Figure 20 (CEAC) and Figure 21 (CEAF).

It is important to understand the apparent difference between these 2 ways of assessing probabilistic model output. The no testing strategy has a high probability of being the best-value option at all assumed values of 1 QALY (indicating that it provided best net benefit in a good proportion of Monte-Carlo simulations). However, at cost-per-QALY thresholds of £14,000 and above, the CEAF indicates that it should not be considered the optimal option, as expected value is less than that achieved with 1 of the testing strategies. This result arises for 2 reasons: firstly, the no testing arm is associated with somewhat greater uncertainty than the testing arms, because it features a much greater proportion of false-negative diagnoses (indeed, 100% of people with coeliac disease effectively have a false-negative diagnosis if no testing is performed). This uncertainty is propagated through the model's lifetime and results in somewhat broader distribution of cost effectiveness results (net monetary benefit) across the probabilistic simulations, with the consequence that, although it has a high probability of being the best value for money, it also has a substantial probability of being the worst value for money. This feature that is not evident on a CEAC (which only focuses on 1 tail of the distribution of value); this is why the CEAF provides a more reliable depiction of decision uncertainty. The second reason that the CEAC, if not carefully interpreted, may appear to overstate the desirability of a no-testing regimen is that, in the collection of simulations in

which no testing is **not** the optimal option, the probability mass for the best option is spread across a large number if possible strategies. The probability that some form of case-finding is superior to no testing is, of course, 1 minus the probability that no testing should be preferred. In other words, the cost-per-QALY threshold at which some form of case-finding has the highest probability of being best-value option is the point at which the probability that no testing should be preferred drops below 50%. In this instance, that threshold is approximately £14,000 per QALY. Again, this apparent distortion is resolved by focussing attention on the CEAF.

Table 17: Base-case cost–utility results – case-finding in first-degree relatives of people with coeliac disease (adults)

	Absolute		Incremental			Net Monetary Benefit	
Name	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)	£20K/QALY	£30K/QALY
NoTest	£9,844	19.8013				£386,182	£584,196
IgGDGP+IgADGP+IgAEMA	£10,037	19.8138	£193	0.0124	ext. dom.	£386,238	£584,376
IgGDGP+IgADGP+IgAEMA+IgATTG	£10,042	19.8132	£198	0.0119	dominated	£386,223	£584,355
IgGDGP+IgAEMA+IgATTG	£10,074	19.8163	£230	0.0149	ext. dom.	£386,252	£584,414
IgGDGP+IgATTG	£10,082	19.8166	£237	0.0153	ext. dom.	£386,251	£584,417
IgGDGP+IgADGP+IgATTG	£10,084	19.8167	£240	0.0153	ext. dom.	£386,250	£584,416
IgGDGP+IgAEMA	£10,086	19.8165	£242	0.0152	dominated	£386,243	£584,408
IgAEMA	£10,097	19.8194	£253	0.0180	ext. dom.	£386,290	£584,484
StepIgATTG_equiv_then_IgAEMA	£10,099	19.8195	£255	0.0182	£13,986	£386,292	£584,487
IgGDGP	£10,100	19.8190	£1	-0.0005	dominated	£386,280	£584,470
BothIgATTG+IgAEMA	£10,105	19.8192	£7	-0.0004	dominated	£386,278	£584,470
StepIgATTG_then_IgAEMA	£10,112	19.8197	£14	0.0002	ext. dom.	£386,282	£584,479
IgATTG	£10,147	19.8203	£48	0.0007	£65,994	£386,258	£584,461
EitherIgATTG+IgAEMA	£10,162	19.8205	£15	0.0002	£75,083	£386,247	£584,452
IgADGP	£10,166	19.8184	£3	-0.0021	dominated	£386,202	£584,385

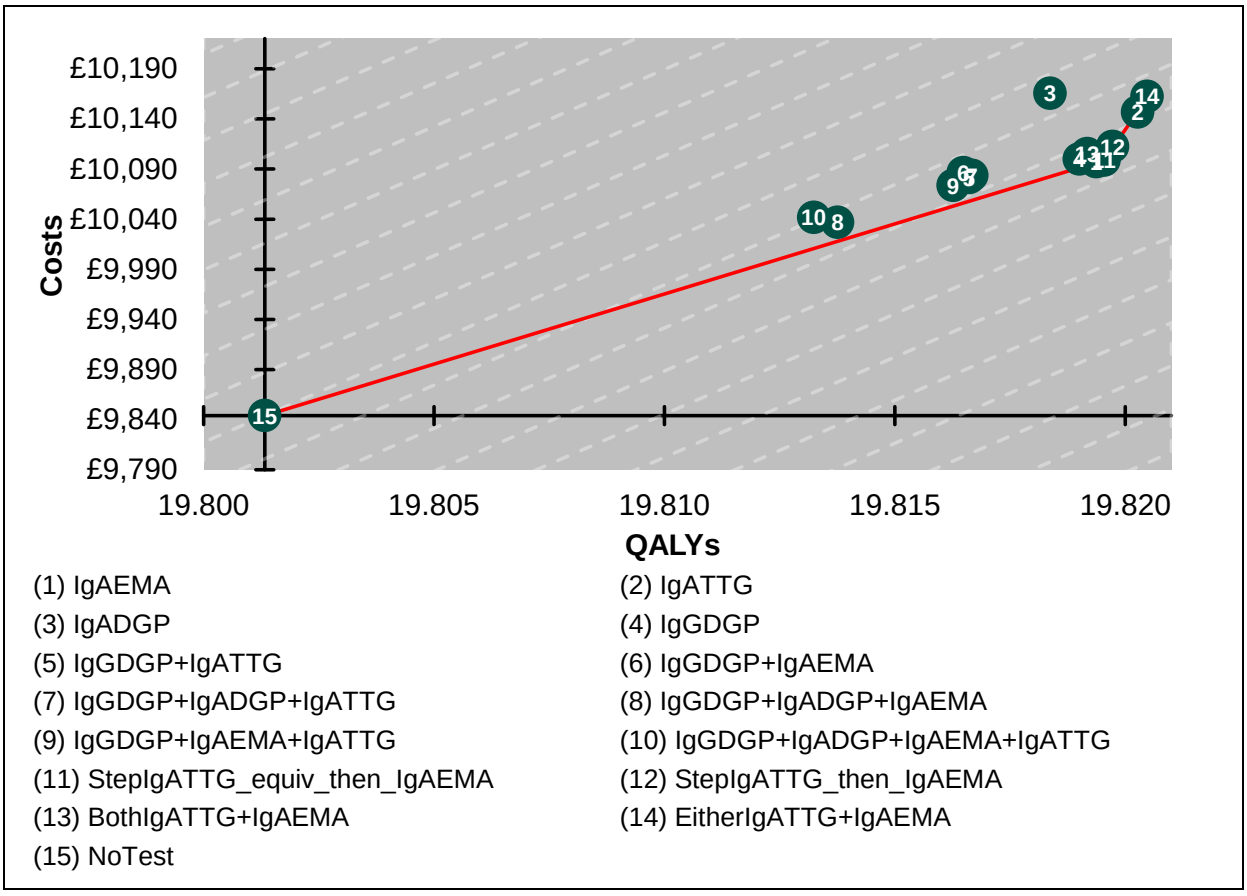
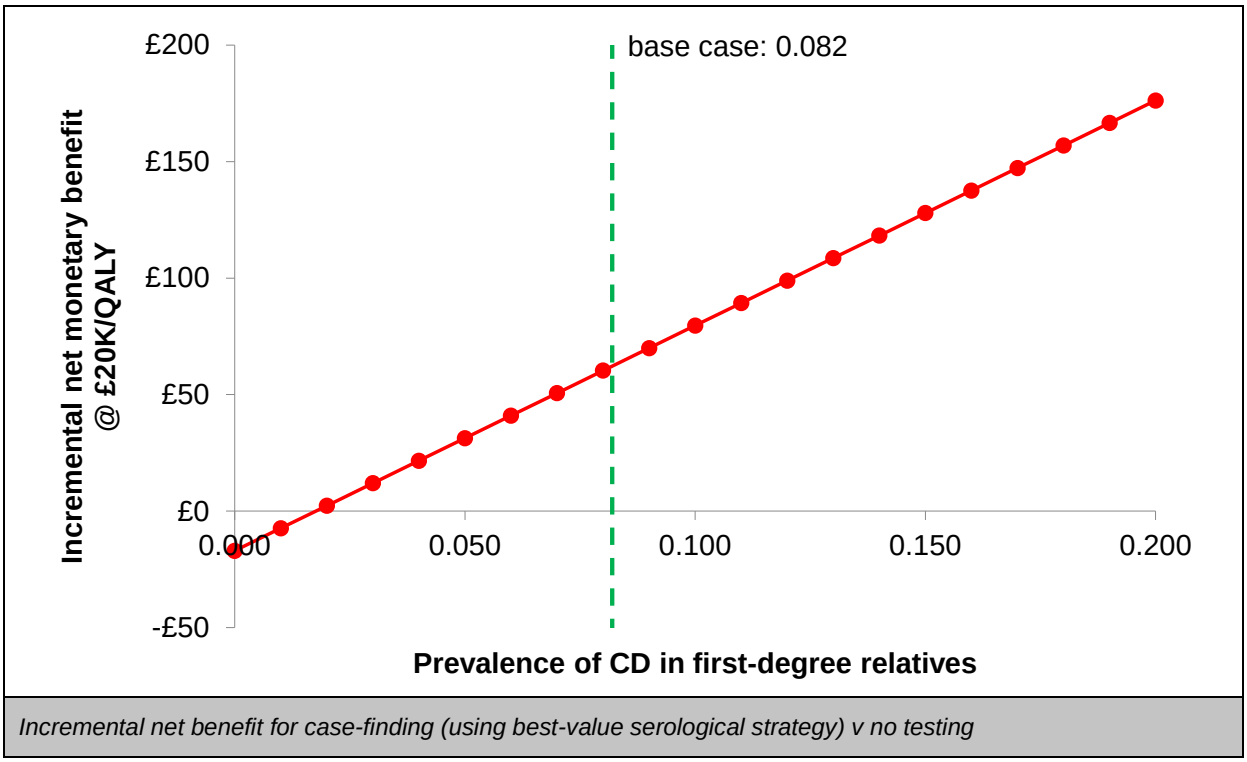
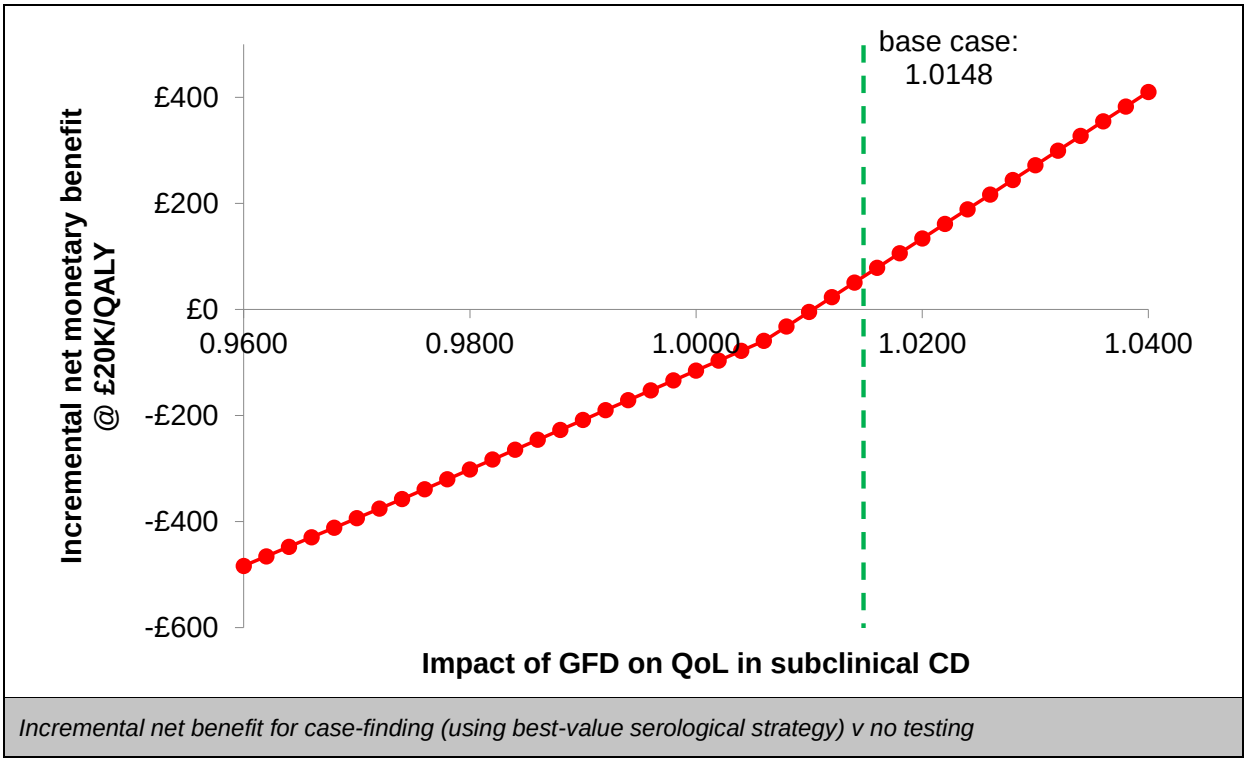


Figure 17: Base-case cost–utility plane – case-finding in first-degree relatives of people with coeliac disease (adults)



Incremental net benefit for case-finding (using best-value serological strategy) v no testing

Figure 18: One-way sensitivity analysis – case-finding in first-degree relatives of people with coeliac disease – prevalence of coeliac disease (adults)



Incremental net benefit for case-finding (using best-value serological strategy) v no testing

Figure 19: One-way sensitivity analysis – case-finding in first-degree relatives of people with coeliac disease – impact of GFD on quality of life of people who have been diagnosed with subclinical coeliac disease (adults)

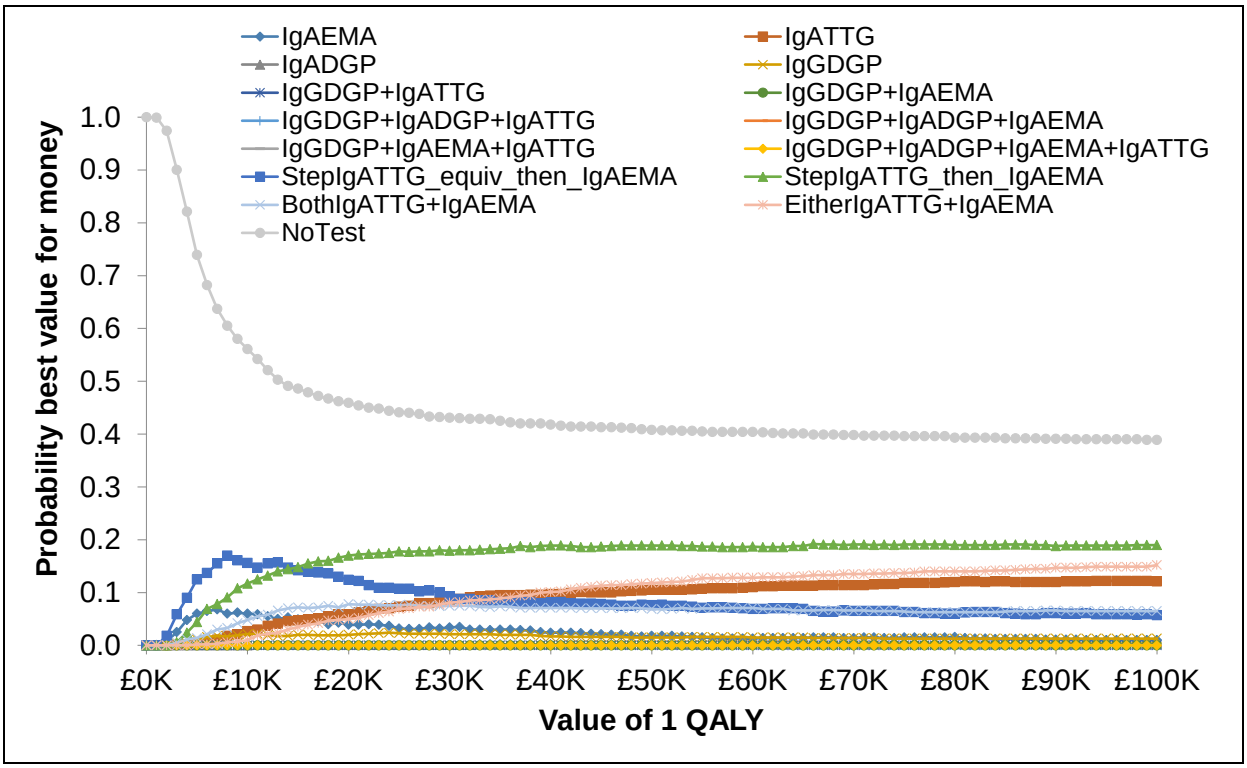


Figure 20: Probabilistic sensitivity analysis – cost-effectiveness acceptability curve: case-finding in first-degree relatives of people with coeliac disease (adults)

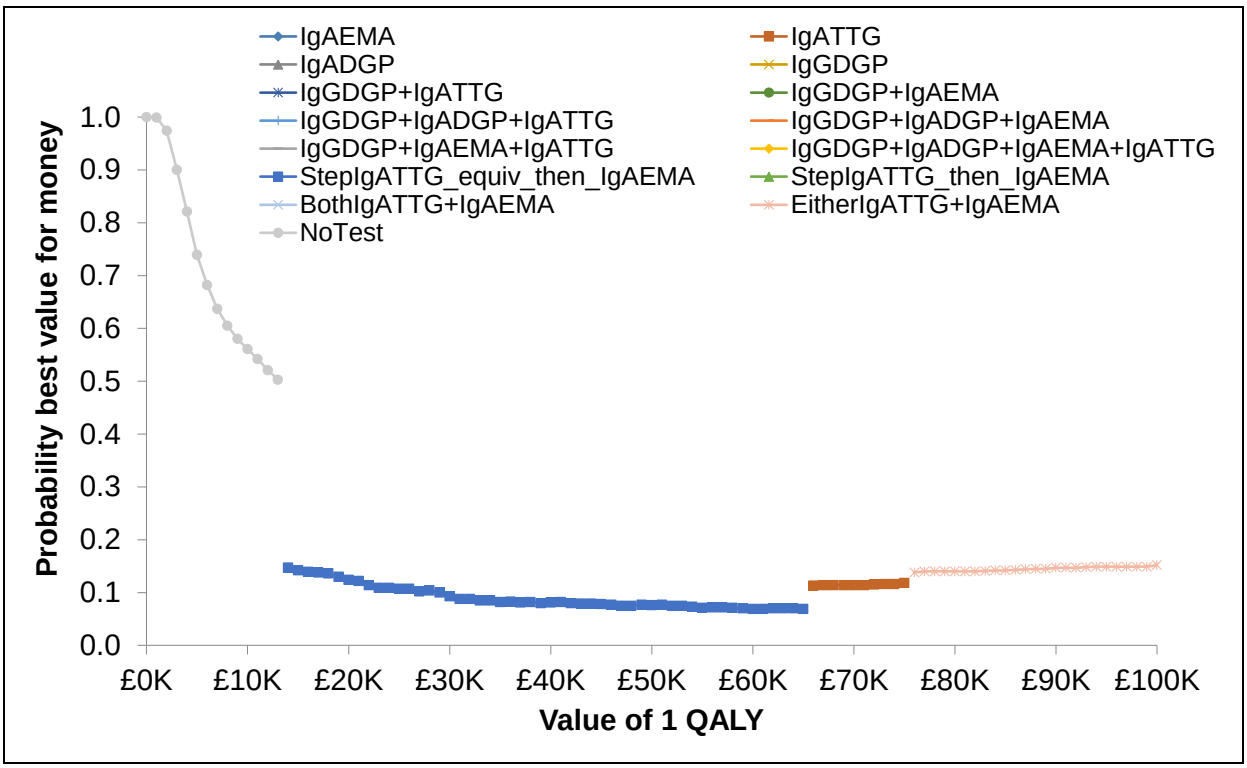


Figure 21: Probabilistic sensitivity analysis – cost-effectiveness acceptability frontier: case-finding in first-degree relatives of people with coeliac disease (adults)

G.2.4.2 First-degree relatives of people with coeliac disease – children

Base-case cost–utility results

Base-case incremental cost–utility results are tabulated in Table 18 and depicted on the cost–utility plane in Figure 22.

As with adults, the cost–utility plane clearly shows that all testing strategies result in improved quality of life at increased cost compared with no testing. Again, the choice of optimal serological strategy closely mirrors that in the symptomatic diagnosis question (see G.1.4.2). The strategy that confers most health benefit is one that combines IgA tTG with IgA EMA and routine HLA testing; however, this approach is associated with incremental costs that push its ICER above £34,000 per QALY, compared with the next-cheapest non-dominated option. Several DGP-containing strategies appear to provide similar value for money, with ICERs in the region of £19,000 per QALY gained compared with no testing.

Deterministic sensitivity analyses

One-way sensitivity analyses exploring the model's sensitivity to key parameters are illustrated below.

Case-finding can be assumed to produce health at a cost of less than £20,000 per QALY if the prevalence of coeliac disease in the tested population exceeds 5%, somewhat lower than the base-case estimate of 6.8% (Figure 23).

The ICER remains below £20,000 as long as it can be assumed that a gluten-free diet improves the health-related quality of life of people with subclinical coeliac disease by 1.36% or more (base-case value 1.48%; Figure 24).

Probabilistic sensitivity analysis

The results of probabilistic sensitivity analysis are shown in Figure 25 (CEAC) and Figure 26 (CEAF). These two graphs have very similar features to those seen in the PSA for case-finding in adult first-degree relatives; for an explanation and discussion, see p. 52.

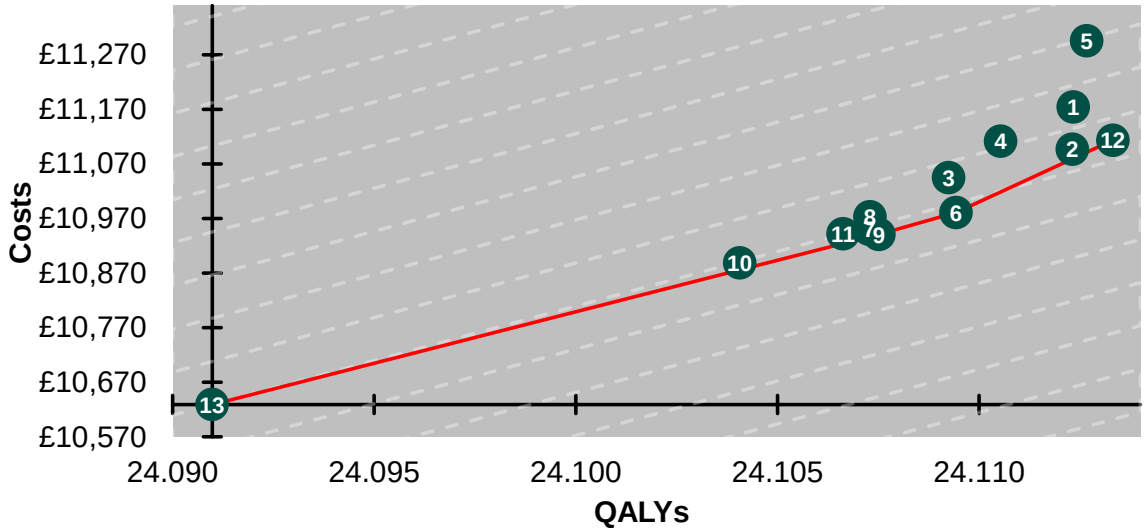
The CEAF indicates that no testing should be considered the optimal option at cost-per-QALY thresholds below £19,000. At this level and above, maximal expected value is achieved with 1 of the testing strategies. Relatedly, the threshold at which some form of case-finding has the highest probability of being best-value option is approximately £16,000 per QALY.

Table 18: Base-case cost–utility results – case-finding in first-degree relatives of people with coeliac disease (children)

	Absolute		Incremental			Net Monetary Benefit	
Name	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)	£20K/QALY	£30K/QALY
NoTest	£10,629	24.0910				£471,190	£712,100
IgGDGP+IgAEMA+IgATTG	£10,889	24.1041	£259	0.0131	ext. dom.	£471,193	£712,233
IgGDGP+IgADGP+IgAEMA	£10,941	24.1075	£312	0.0165	£18,844	£471,209	£712,285
IgGDGP+IgADGP+IgAEMA+IgATTG	£10,942	24.1066	£1	-0.0009	dominated	£471,190	£712,257
IgGDGP+IgAEMA	£10,950	24.1073	£10	-0.0002	dominated	£471,195	£712,268
IgGDGP+IgADGP+IgATTG	£10,973	24.1073	£32	-0.0002	dominated	£471,173	£712,246
IgGDGP+IgATTG	£10,981	24.1094	£40	0.0019	£21,016	£471,207	£712,302
IgADGP	£11,045	24.1092	£64	-0.0002	dominated	£471,140	£712,232

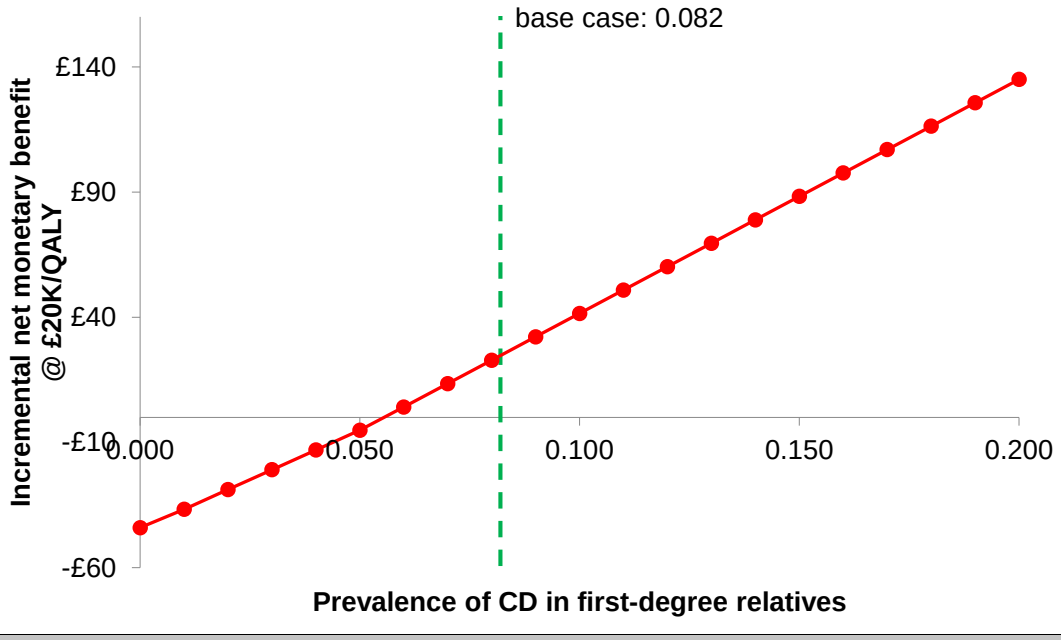
Name	Absolute		Incremental			Net Monetary Benefit	
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)	£20K/QALY	£30K/QALY
IgATTG	£11,097	24.1123	£116	0.0029	ext. dom.	£471,150	£712,273
IgGDGP	£11,112	24.1105	£130	0.0011	dominated	£471,099	£712,205
IgATTG+IgAEMA+HLA	£11,114	24.1133	£132	0.0039	£34,054	£471,153	£712,286
IgAEMA	£11,174	24.1123	£61	-0.0010	dominated	£471,072	£712,196
HLA	£11,296	24.1127	£182	-0.0006	dominated	£470,958	£712,084

1



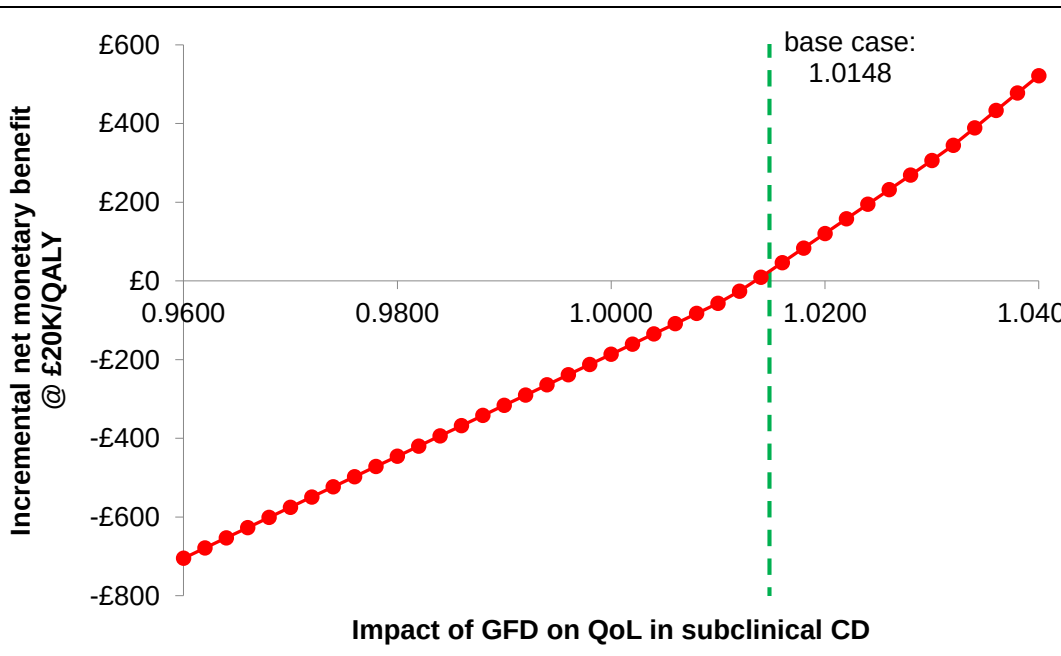
2 **Figure 22: Base-case cost–utility plane – case-finding in first-degree relatives of**
3 **people with coeliac disease (children)**

4



Incremental net benefit for case-finding (using best-value serological strategy) v no testing

Figure 23: One-way sensitivity analysis – case-finding in first-degree relatives of people with coeliac disease – prevalence of coeliac disease (children)



Incremental net benefit for case-finding (using best-value serological strategy) v no testing

Figure 24: One-way sensitivity analysis – case-finding in first-degree relatives of people with coeliac disease – impact of GFD on quality of life of people who have been diagnosed with subclinical coeliac disease (children)

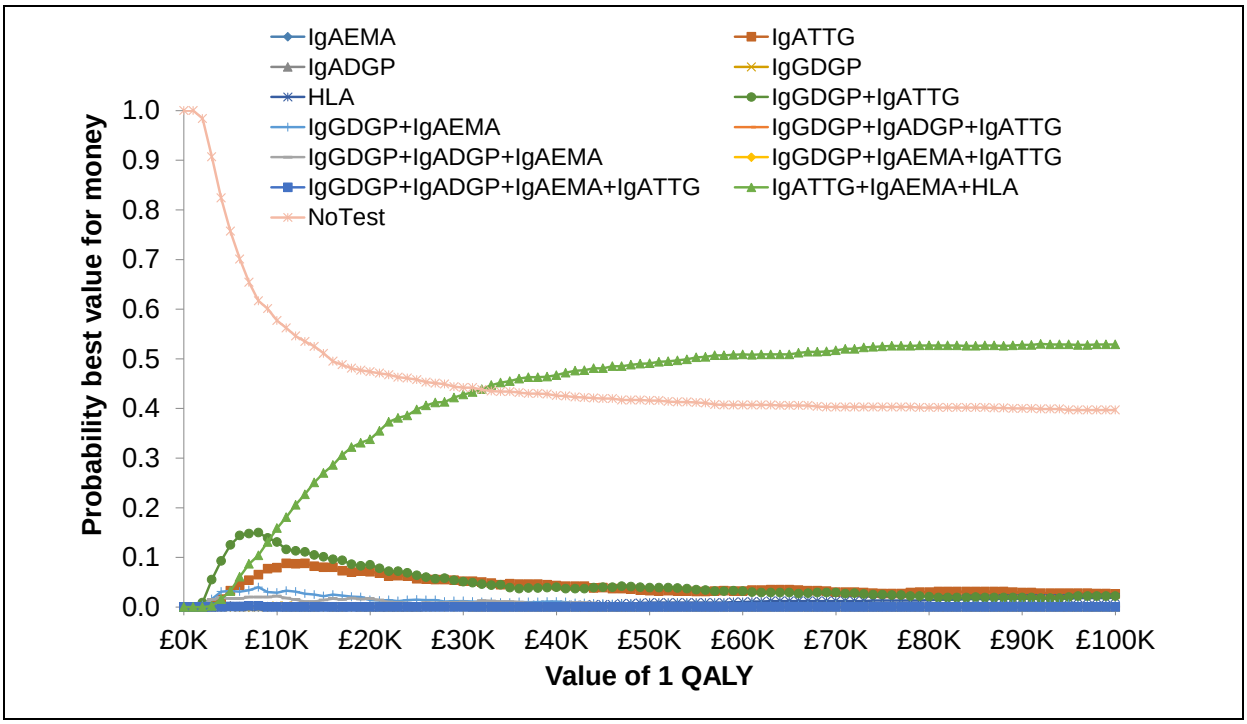


Figure 25: Probabilistic sensitivity analysis – cost-effectiveness acceptability curve: case-finding in first-degree relatives of people with CD (children)

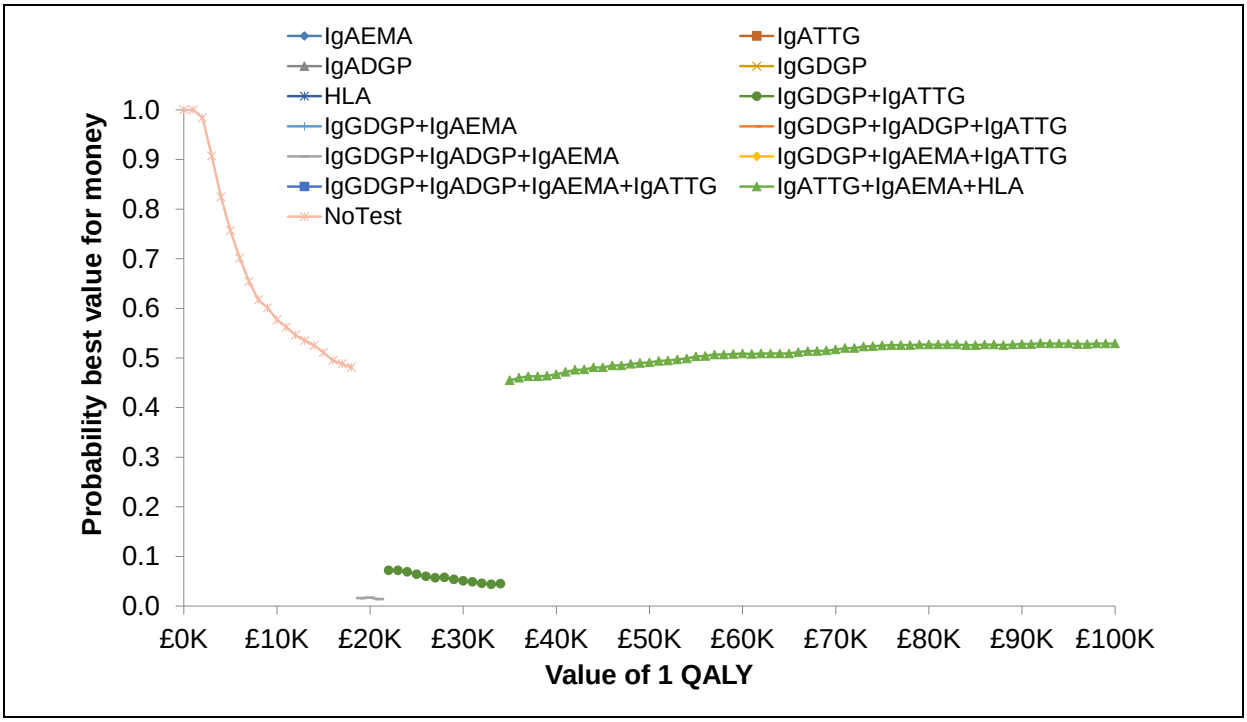


Figure 26: Probabilistic sensitivity analysis – cost-effectiveness acceptability frontier: case-finding in first-degree relatives of people with CD (children)

G.2.4.3 Type 1 diabetes – adults

Base-case cost–utility results

Base-case incremental cost–utility results are tabulated in Table 19 and depicted on the cost–utility plane in Figure 27.

As with other case-finding populations, all testing strategies result in improved quality of life at increased cost compared with no testing, and the choice of optimal serological strategy closely mirrors that in the symptomatic diagnosis question (see G.1.4.2). The most sensitive strategies (IgA tTG alone and EitherIgATTG+IgAEMA [that is, considering people serologically positive if they are positive on either IgA tTG or IgA EMA]) produce greatest health gains, but the incremental benefits are small and come at substantial incremental cost, when compared with the recommended strategy in symptomatic people (that is, one that tests IgA tTG in all people and reserves IgA EMA to classify cases in which IgA tTG results are weakly positive). This approach has an ICER of £17,100 per QALY gained compared with no testing.

Deterministic sensitivity analyses

One-way sensitivity analyses exploring the model's sensitivity to key parameters are illustrated below.

Case-finding can be assumed to produce health at a cost of less than £20,000 per QALY if the prevalence of coeliac disease in the tested population exceeds 3.4% (Figure 28). This threshold exceeds the base-case value of 3.3%, which is an unexpected finding, given that the best-value case-finding strategy is associated with an ICER of less than £20,000 per QALY compared with no testing. This result arises because of nonlinearity in the model: the sensitivity analyses are based on deterministic evaluations of the model, whereas the base-case cost–utility results represent the mean of all probabilistic simulations. The probabilistic approach provides a more accurate estimate of true expected value, given parameter uncertainty, but may be somewhat different from deterministic results in nonlinear models (Markov models frequently have this property, as is the case here).

The ICER remains below £20,000 as long as it can be assumed that a gluten-free diet improves the health-related quality of life of people with subclinical coeliac disease by 1.50% or more (base-case value 1.48%; Figure 29). Again, nonlinearity in the model produces a slightly paradoxical result, here.

Probabilistic sensitivity analysis

The results of probabilistic sensitivity analysis are shown in Figure 30 (CEAC) and Figure 31 (CEAF). These two graphs have very similar features to those seen in the PSA for case-finding in adult first-degree relatives; for an explanation and discussion, see p. 52.

The CEAF indicates that no testing should be considered the optimal option at cost-per-QALY thresholds below £18,000. At this level and above, maximal expected value is achieved with 1 of the testing strategies. Relatedly, the threshold at which some form of case-finding has the highest probability of being best-value option is also approximately £18,000 per QALY.

Table 19: Base-case cost–utility results – case-finding in type 1 diabetes (adults)

	Absolute		Incremental			Net Monetary Benefit	
Name	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)	£20K/QALY	£30K/QALY
NoTest	£8,118	17.2691				£337,265	£509,956
IgGDGP+IgADGP+IgAEMA	£8,210	17.2731	£92	0.0039	ext. dom.	£337,251	£509,982
StepIgATTG_equiv_then_IgAEMA	£8,217	17.2749	£99	0.0058	£17,094	£337,281	£510,031
IgAEMA	£8,218	17.2749	£1	-0.0001	dominated	£337,279	£510,028
IgGDGP+IgADGP+IgAEMA+IgATTG	£8,219	17.2730	£2	-0.0020	dominated	£337,240	£509,970
IgGDGP+IgAEMA+IgATTG	£8,223	17.2738	£6	-0.0011	dominated	£337,254	£509,992
IgGDGP	£8,224	17.2747	£7	-0.0003	dominated	£337,269	£510,016
BothIgATTG+IgAEMA	£8,225	17.2748	£8	-0.0001	dominated	£337,271	£510,019
IgGDGP+IgATTG	£8,227	17.2739	£10	-0.0010	dominated	£337,251	£509,991
StepIgATTG_then_IgAEMA	£8,227	17.2750	£10	0.0000	£274,198	£337,272	£510,021
IgGDGP+IgADGP+IgATTG	£8,228	17.2741	£0	-0.0009	dominated	£337,253	£509,994
IgGDGP+IgAEMA	£8,232	17.2739	£4	-0.0010	dominated	£337,247	£509,986
IgATTG	£8,256	17.2750	£29	0.0001	ext. dom.	£337,244	£509,995
EitherIgATTG+IgAEMA	£8,271	17.2751	£43	0.0001	£334,840	£337,231	£509,982
IgADGP	£8,296	17.2742	£25	-0.0009	dominated	£337,188	£509,931

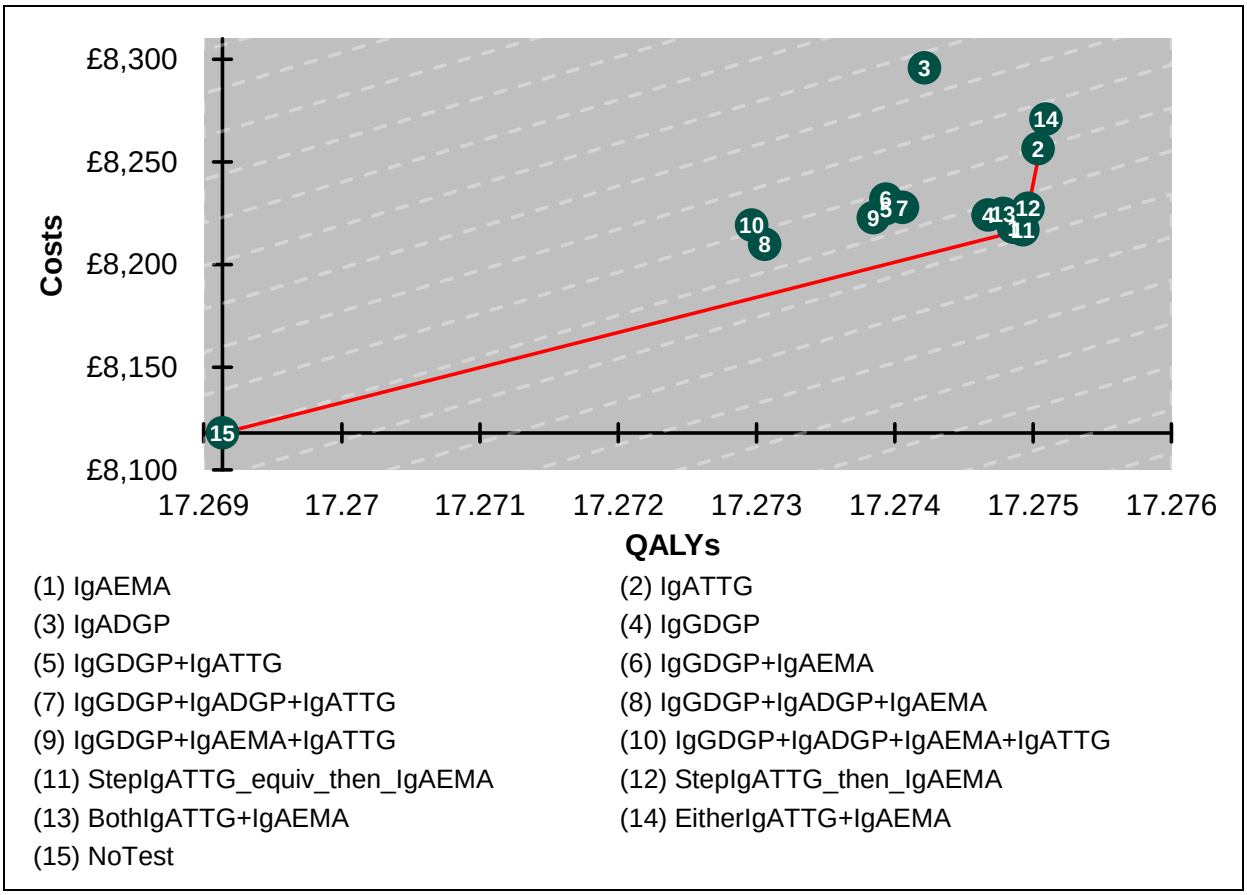
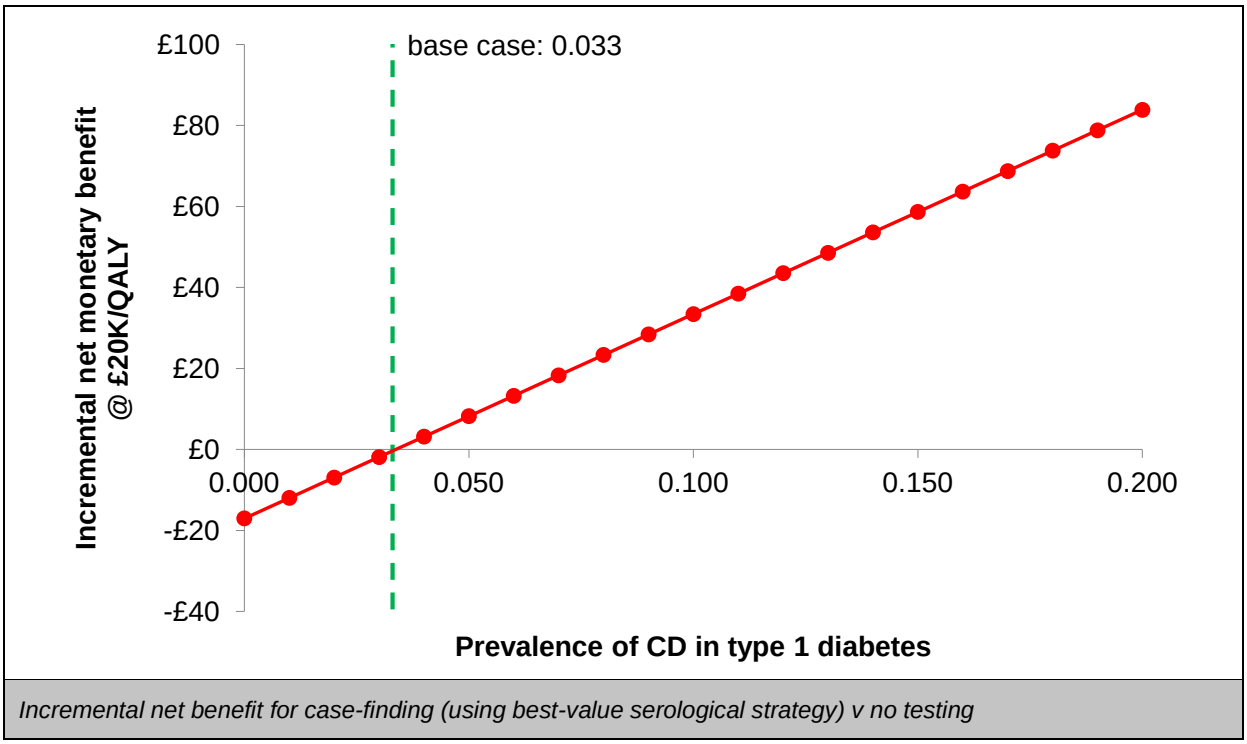
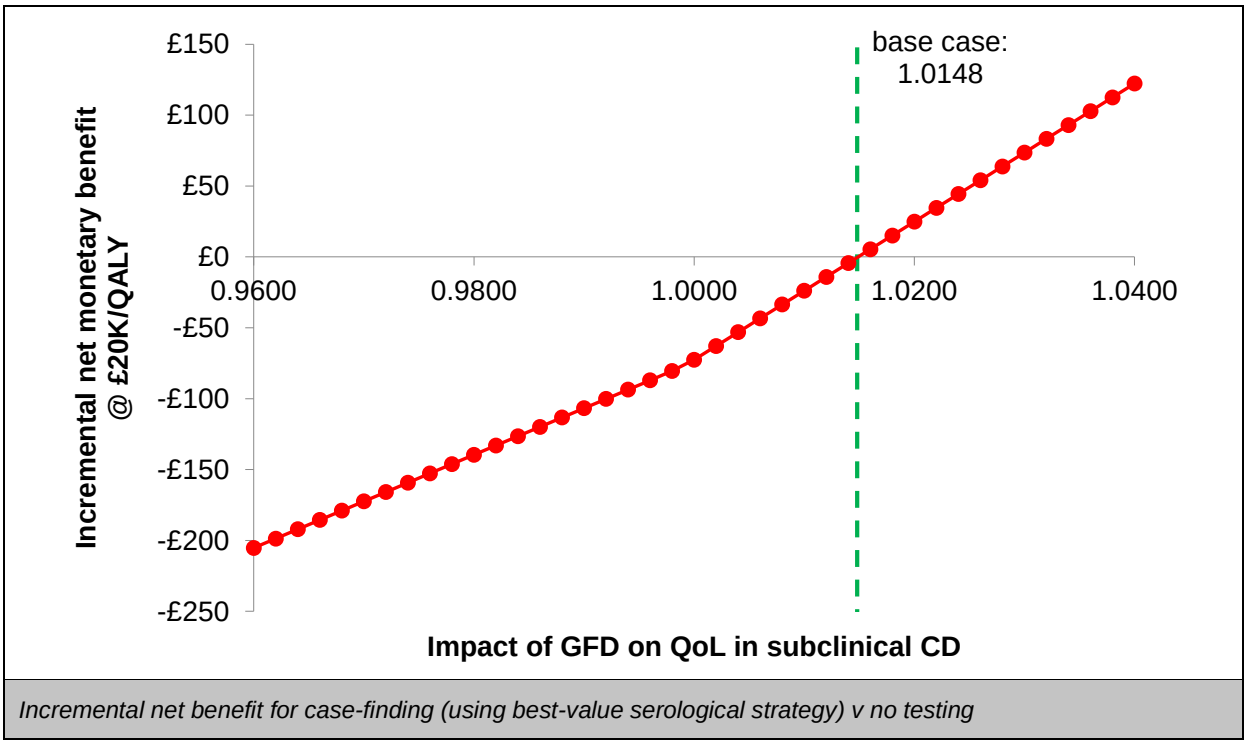


Figure 27: Base-case cost–utility plane – case-finding in type 1 diabetes (adults)



Incremental net benefit for case-finding (using best-value serological strategy) v no testing

Figure 28: One-way sensitivity analysis – case-finding in type 1 diabetes – prevalence of coeliac disease (adults)



Incremental net benefit for case-finding (using best-value serological strategy) v no testing

Figure 29: One-way sensitivity analysis – case-finding in type 1 diabetes – impact of GFD on quality of life of people who have been diagnosed with subclinical coeliac disease (adults)

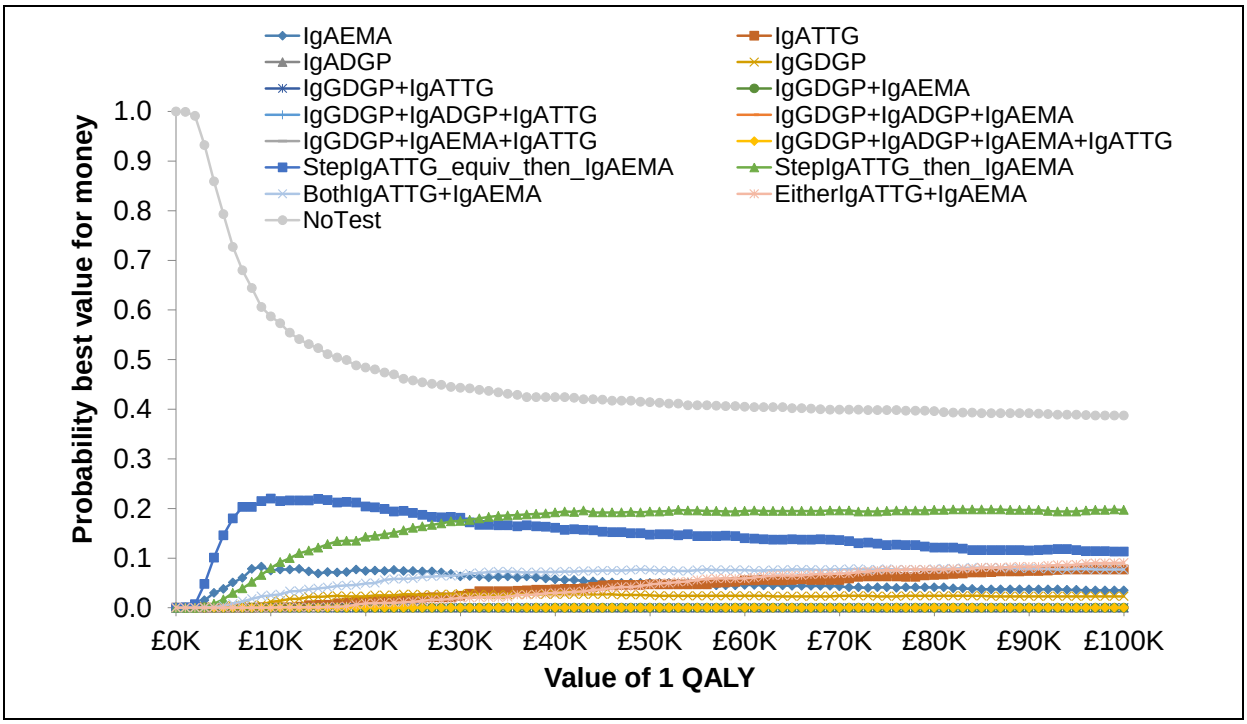


Figure 30: Probabilistic sensitivity analysis – cost-effectiveness acceptability curve: case-finding in type 1 diabetes (adults)

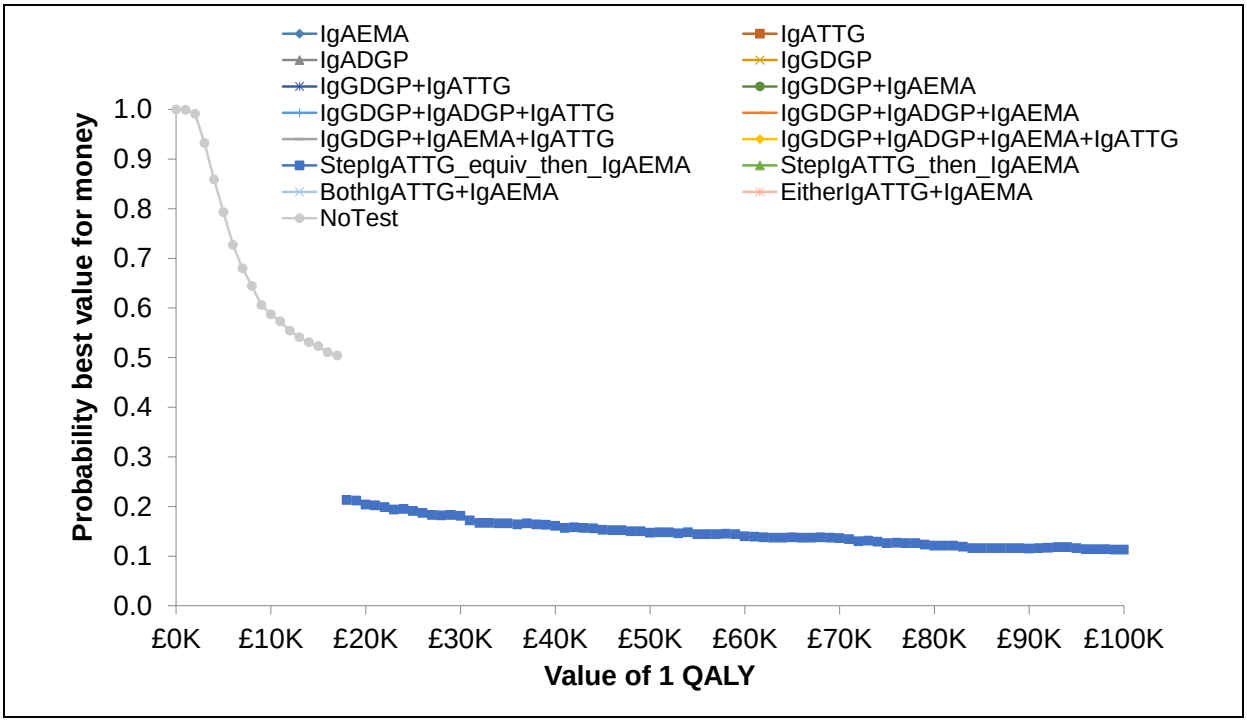


Figure 31: Probabilistic sensitivity analysis – cost-effectiveness acceptability frontier: case-finding in type 1 diabetes (adults)

G.2.4.4 Type 1 diabetes – children

Base-case cost–utility results

Base-case incremental cost–utility results are tabulated in Table 20 and depicted on the cost–utility plane in Figure 32.

As with other case-finding populations, all testing strategies result in improved quality of life at increased cost compared with no testing, and the choice of optimal serological strategy closely mirrors that in the symptomatic diagnosis question (see G.1.4.2). The strategy that confers most health benefit is one that combines IgA tTG with IgA EMA and routine HLA testing; however, this approach is associated with incremental costs that push its ICER up to around £60,000 per QALY, compared with the next-cheapest non-dominated option. Several DGP-containing strategies appear to provide similar value for money, with ICERs in the region of £20–25,000 per QALY gained compared with no testing.

Deterministic sensitivity analyses

One-way sensitivity analyses exploring the model's sensitivity to key parameters are illustrated below.

Case-finding can be assumed to produce health at a cost of less than £20,000 per QALY if the prevalence of coeliac disease in the tested population exceeds 9% (base-case value 3.3%; Figure 33).

The ICER falls below £20,000 if it can be assumed that a gluten-free diet improves the health-related quality of life of people with subclinical coeliac disease by 1.94% or more (base-case value 1.48%; Figure 34).

Probabilistic sensitivity analysis

The results of probabilistic sensitivity analysis are shown in Figure 35 (CEAC) and Figure 36 (CEAF). These two graphs have very similar features to those seen in the PSA for case-finding in adult first-degree relatives; for an explanation and discussion, see p. 52.

The CEAF indicates that no testing should be considered the optimal option at cost-per-QALY thresholds below £21,000. At this level and above, maximal expected value is achieved with 1 of the testing strategies. Relatedly, the threshold at which some form of case-finding has the highest probability of being best-value option is approximately £22,000 per QALY.

Table 20: Base-case cost–utility results – case-finding in type 1 diabetes (children)

Name	Absolute		Incremental			Net Monetary Benefit	
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)	£20K/QALY	£30K/QALY
NoTest	£9,620	22.7910				£446,200	£674,110
IgGDGP+IgAEMA+IgATTG	£9,744	22.7965	£124	0.0055	ext. dom.	£446,187	£674,153
IgGDGP+IgADGP+IgAEMA	£9,764	22.7980	£145	0.0070	£20,564	£446,196	£674,177
IgGDGP+IgADGP+IgAEMA+IgATTG	£9,772	22.7977	£8	-0.0003	dominated	£446,183	£674,160
IgGDGP+IgAEMA	£9,775	22.7978	£10	-0.0002	dominated	£446,182	£674,160
IgGDGP+IgATTG	£9,783	22.7988	£19	0.0008	£23,410	£446,194	£674,182
IgGDGP+IgADGP+IgATTG	£9,797	22.7979	£13	-0.0009	dominated	£446,162	£674,141
IgADGP	£9,855	22.7985	£71	-0.0004	dominated	£446,115	£674,100
IgATTG	£9,871	22.7999	£88	0.0010	ext. dom.	£446,126	£674,125
IgATTG+IgAEMA+HLA	£9,880	22.8005	£97	0.0016	£59,681	£446,129	£674,134
IgGDGP	£9,908	22.7991	£27	-0.0014	dominated	£446,075	£674,066
IgAEMA	£9,954	22.7997	£74	-0.0007	dominated	£446,040	£674,038
HLA	£10,077	22.7997	£196	-0.0007	dominated	£445,918	£673,915

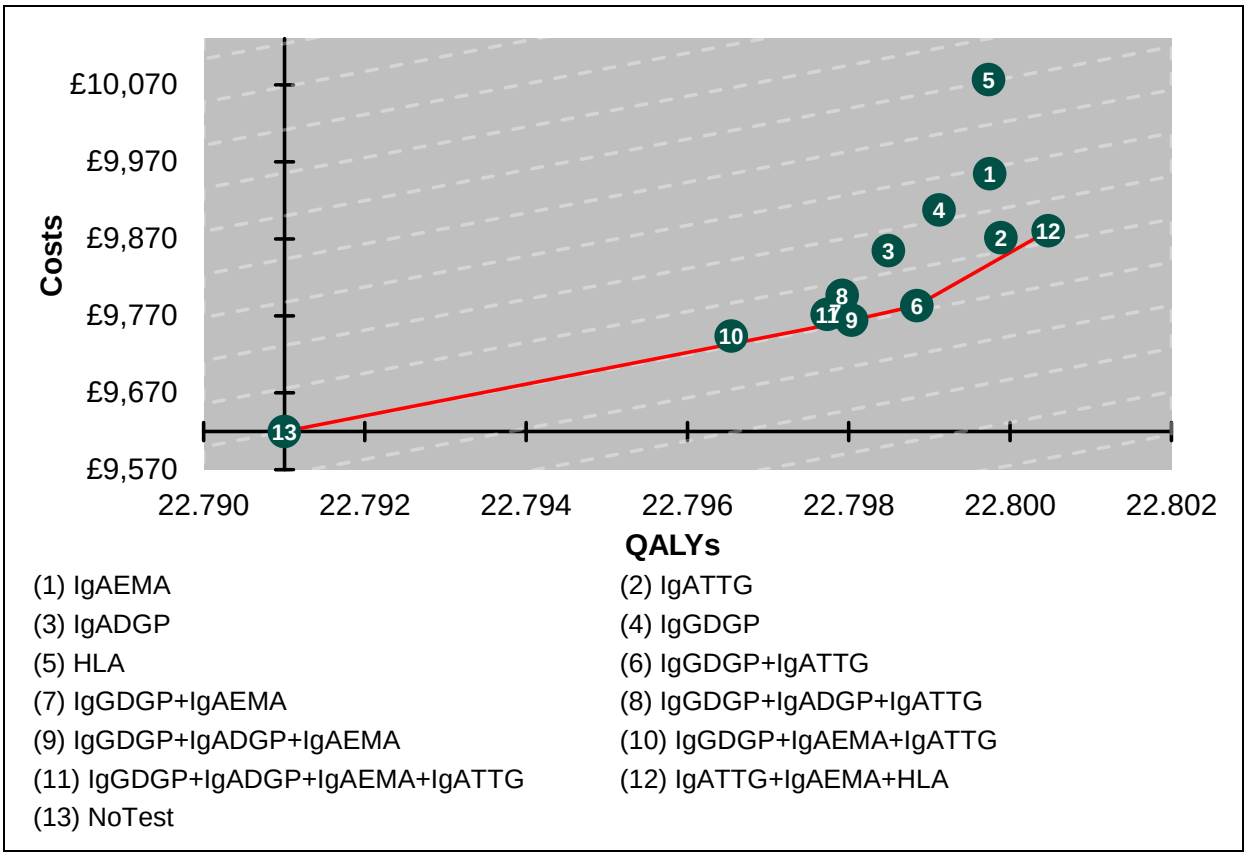
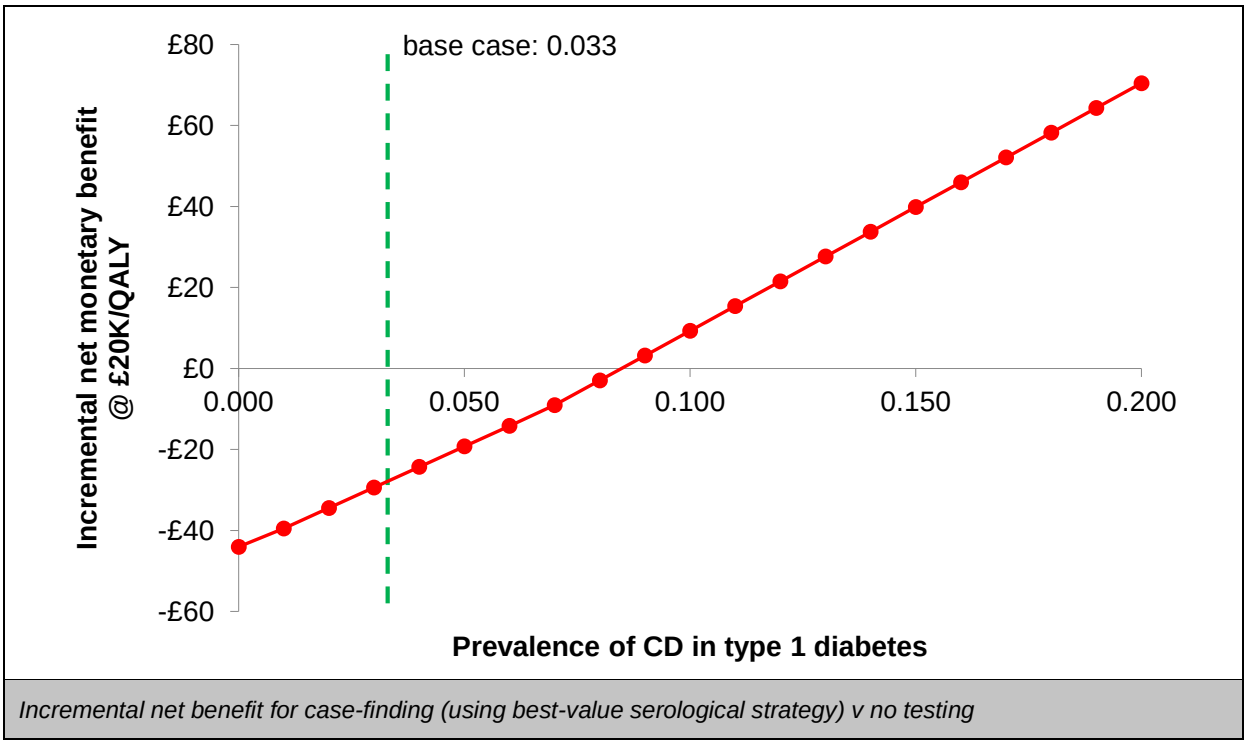
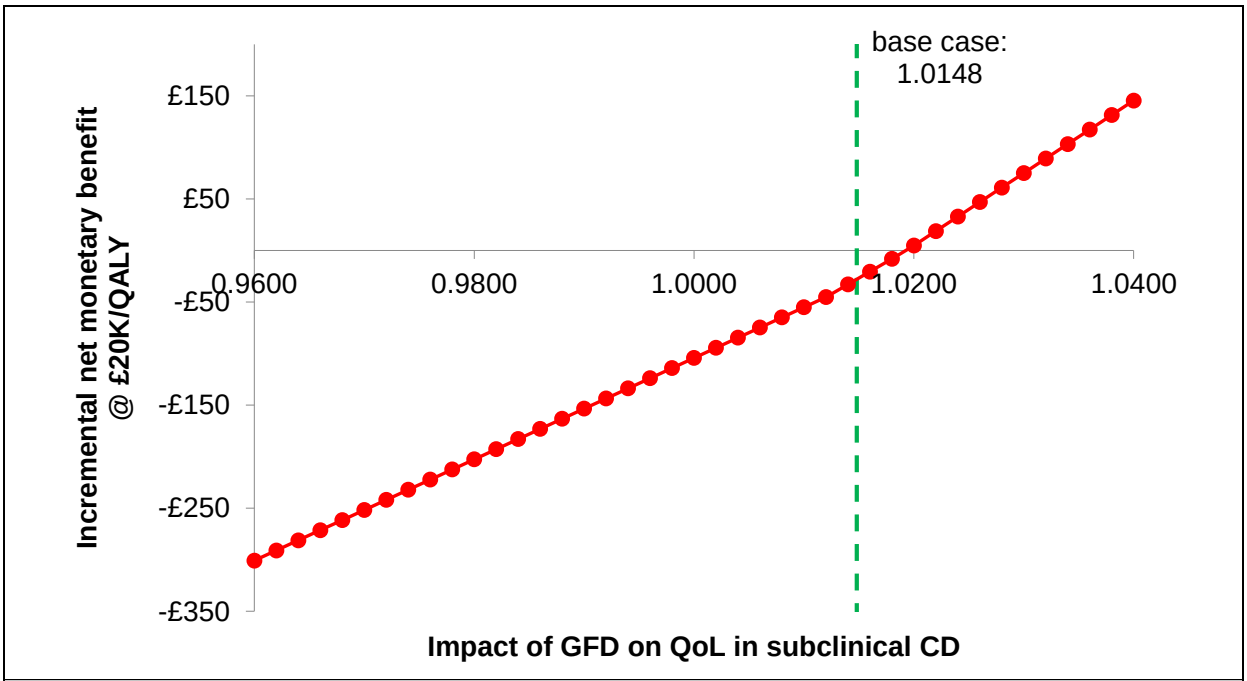


Figure 32: Base-case cost–utility plane – case-finding in type 1 diabetes (children)



Incremental net benefit for case-finding (using best-value serological strategy) v no testing

Figure 33: One-way sensitivity analysis – case-finding in type 1 diabetes – prevalence of coeliac disease (children)



Incremental net benefit for case-finding (using best-value serological strategy) v no testing

Figure 34: One-way sensitivity analysis – case-finding in type 1 diabetes – impact of GFD on quality of life of people who have been diagnosed with subclinical coeliac disease (children)

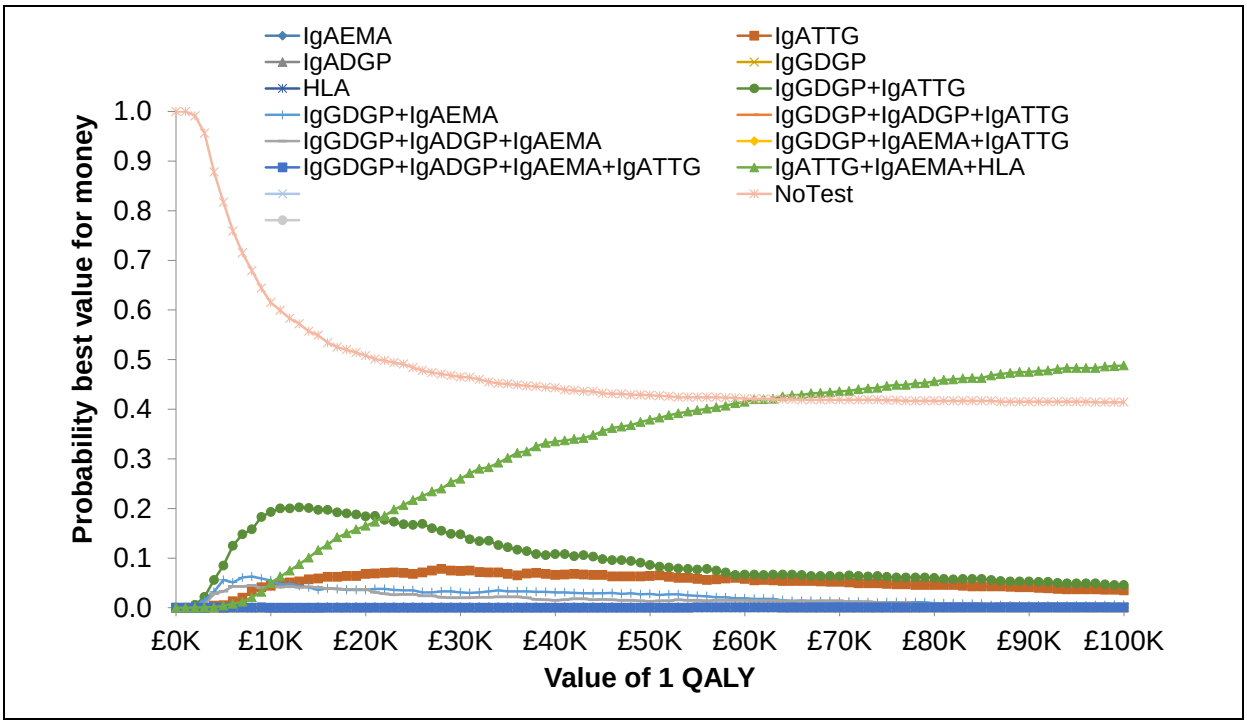


Figure 35: Probabilistic sensitivity analysis – cost-effectiveness acceptability curve: case-finding in type 1 diabetes (children)

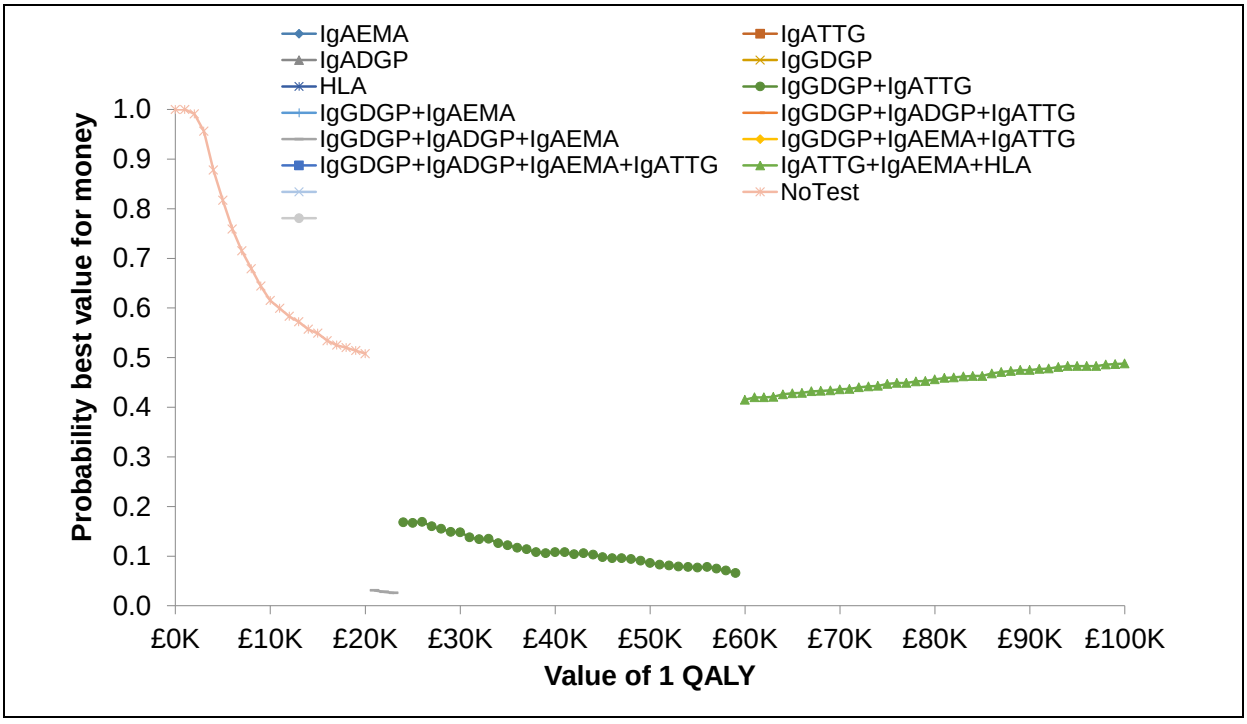


Figure 36: Probabilistic sensitivity analysis – cost-effectiveness acceptability frontier: case-finding in type 1 diabetes (children)

G.2.4.5 Autoimmune thyroid disease – adults

Base-case cost–utility results

Base-case incremental cost–utility results are tabulated in Table 21 and depicted on the cost–utility plane in Figure 37.

As with other case-finding populations, all testing strategies result in improved quality of life at increased cost compared with no testing, and the choice of optimal serological strategy closely mirrors that in the symptomatic diagnosis question (see G.1.4.2). The most sensitive strategies (IgA tTG alone and EitherIgATTG+IgAEMA [that is, considering people serologically positive if they are positive on either IgA tTG or IgA EMA]) produce greatest health gains, but the incremental benefits are small and come at substantial incremental cost, when compared with the recommended strategy in symptomatic people (that is, one that tests IgA tTG in all people and reserves IgA EMA to classify cases in which IgA tTG results are weakly positive). This approach has an ICER of £26,000 per QALY gained compared with no testing.

Deterministic sensitivity analyses

One-way sensitivity analyses exploring the model's sensitivity to key parameters are illustrated below.

Case-finding can be assumed to produce health at a cost of less than £20,000 per QALY if the prevalence of coeliac disease in the tested population exceeds 4.9% (base-case value 2.4%; Figure 38).

The ICER falls below £20,000 if it can be assumed that a gluten-free diet improves the health-related quality of life of people with subclinical coeliac disease by 1.74% or more (base-case value 1.48%; Figure 39).

Probabilistic sensitivity analysis

The results of probabilistic sensitivity analysis are shown in Figure 40 (CEAC) and Figure 41 (CEAF). These two graphs have very similar features to those seen in the PSA for case-finding in adult first-degree relatives; for an explanation and discussion, see p. 52.

The CEAF indicates that no testing should be considered the optimal option at cost-per-QALY thresholds below £26,000. At this level and above, maximal expected value is achieved with 1 of the testing strategies. Relatedly, the threshold at which some form of case-finding has the highest probability of being best-value option is approximately £24,000 per QALY.

Table 21: Base-case cost–utility results – case-finding in autoimmune thyroid disease (adults)

Name	Absolute		Incremental			Net Monetary Benefit	
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)	£20K/QALY	£30K/QALY
NoTest	£9,566	19.7427				£385,289	£582,716
IgGDGP+IgADGP+IgAEMA	£9,648	19.7449	£83	0.0022	ext. dom.	£385,250	£582,699
StepIgATTG_equiv_then_IgAEMA	£9,649	19.7459	£84	0.0032	£25,974	£385,269	£582,729
IgAEMA	£9,650	19.7458	£1	-0.0001	dominated	£385,267	£582,725
IgGDGP	£9,657	19.7458	£8	-0.0002	dominated	£385,258	£582,716
BothIgATTG+IgAEMA	£9,658	19.7459	£8	-0.0001	dominated	£385,260	£582,719
IgGDGP+IgADGP+IgAEMA+IgATTG	£9,658	19.7448	£9	-0.0011	dominated	£385,239	£582,687
IgGDGP+IgAEMA+IgATTG	£9,658	19.7453	£9	-0.0006	dominated	£385,247	£582,700
StepIgATTG_then_IgAEMA	£9,659	19.7459	£10	0.0000	£4,622,040	£385,259	£582,719
IgGDGP+IgADGP+IgATTG	£9,663	19.7454	£4	-0.0005	dominated	£385,246	£582,700
IgGDGP+IgATTG	£9,663	19.7453	£4	-0.0006	dominated	£385,243	£582,696
IgGDGP+IgAEMA	£9,667	19.7453	£8	-0.0006	dominated	£385,239	£582,693
IgATTG	£9,688	19.7459	£28	-0.0001	dominated	£385,230	£582,688
EitherIgATTG+IgAEMA	£9,702	19.7459	£43	-0.0001	dominated	£385,215	£582,674
IgADGP	£9,730	19.7453	£71	-0.0007	dominated	£385,176	£582,628

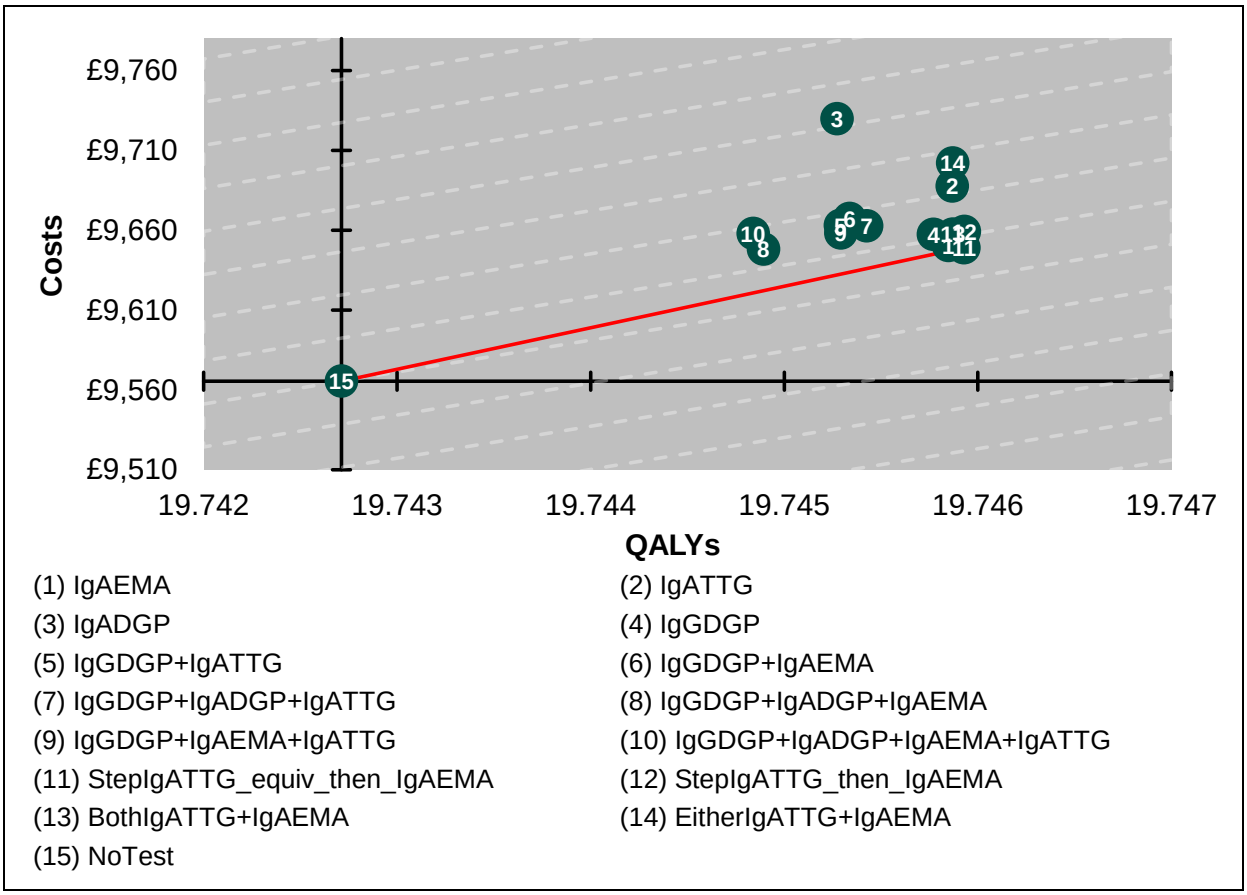
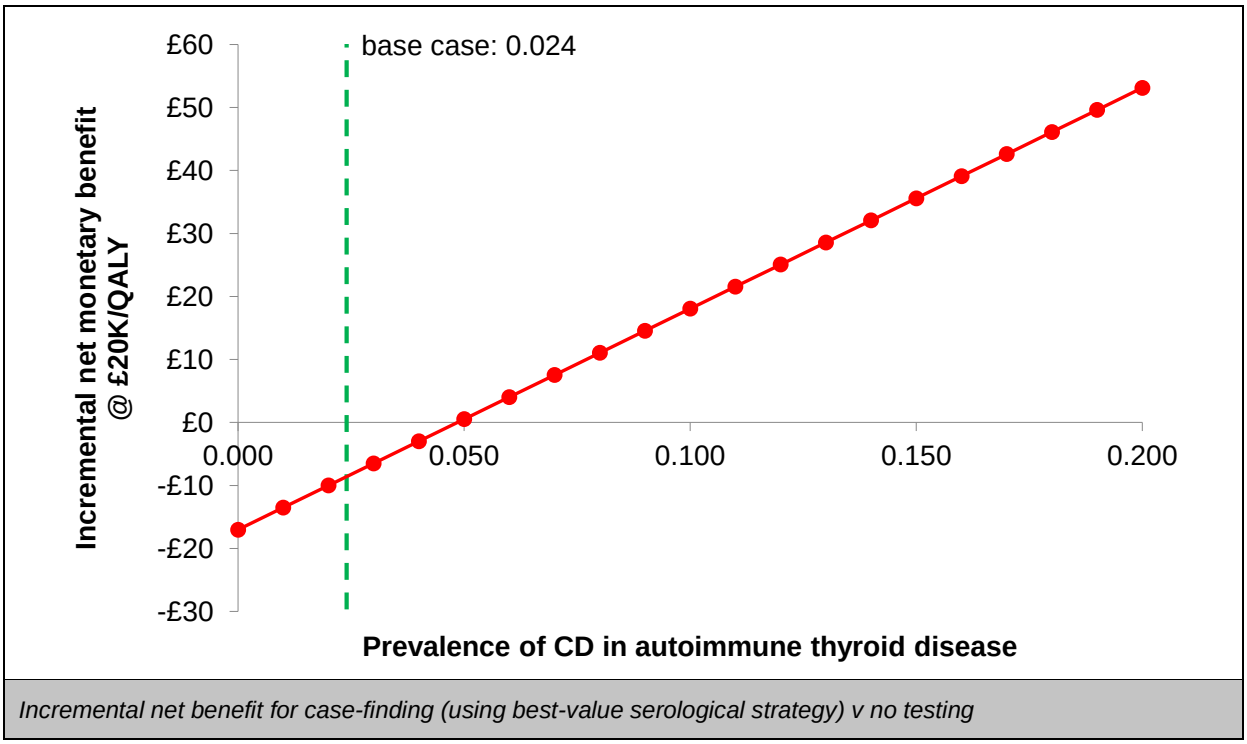
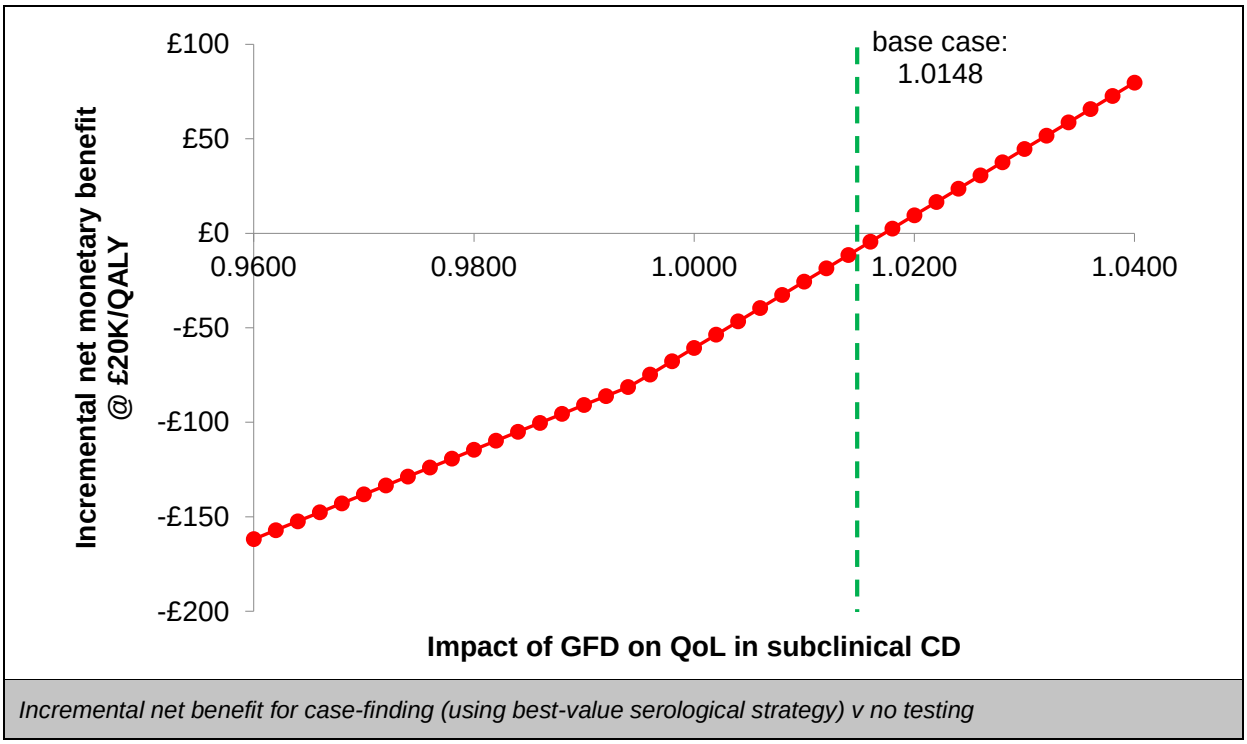


Figure 37: Base-case cost–utility plane – case-finding in autoimmune thyroid disease (adults)



Incremental net benefit for case-finding (using best-value serological strategy) v no testing

Figure 38: One-way sensitivity analysis – case-finding in autoimmune thyroid disease – prevalence of coeliac disease (adults)



Incremental net benefit for case-finding (using best-value serological strategy) v no testing

Figure 39: One-way sensitivity analysis – case-finding in autoimmune thyroid disease – impact of GFD on quality of life of people who have been diagnosed with subclinical coeliac disease (adults)

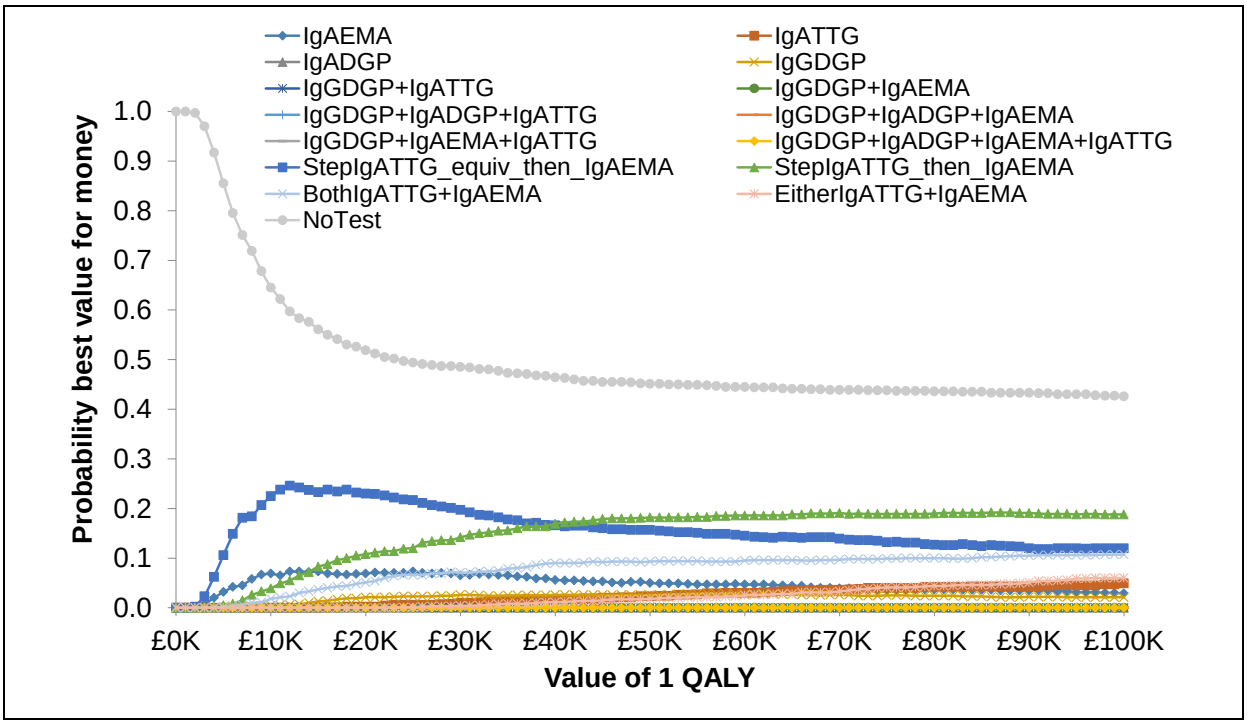


Figure 40: Probabilistic sensitivity analysis – cost-effectiveness acceptability curve: case-finding in autoimmune thyroid disease (adults)

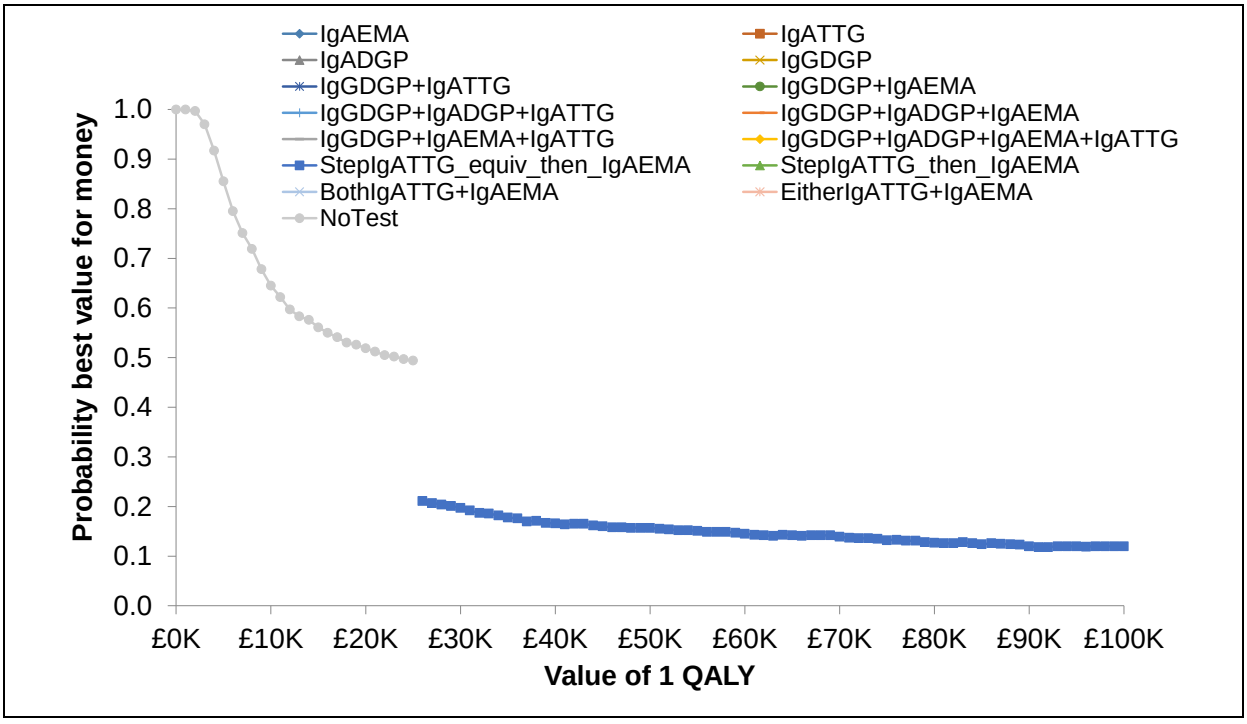


Figure 41: Probabilistic sensitivity analysis – cost-effectiveness acceptability frontier: case-finding in autoimmune thyroid disease (adults)

G.2.4.6 Autoimmune thyroid disease – children

Base-case cost–utility results

Base-case incremental cost–utility results are tabulated in Table 22 and depicted on the cost–utility plane in Figure 42.

As with other case-finding populations, all testing strategies result in improved quality of life at increased cost compared with no testing, and the choice of optimal serological strategy closely mirrors that in the symptomatic diagnosis question (see G.1.4.2). The strategy that confers most health benefit is one that combines IgA tTG with IgA EMA and routine HLA testing; however, this approach is associated with incremental costs that push its ICER close to £100,000 per QALY, compared with the next-cheapest non-dominated option. Several DGP-containing strategies appear to provide similar value for money, with ICERs in the region of £25–35,000 per QALY gained compared with no testing.

Deterministic sensitivity analyses

One-way sensitivity analyses exploring the model's sensitivity to key parameters are illustrated below.

Case-finding can be assumed to produce health at a cost of less than £20,000 per QALY if the prevalence of coeliac disease in the tested population exceeds 17% (base-case value 3.1%; Figure 43).

The ICER falls below £20,000 if it can be assumed that a gluten-free diet improves the health-related quality of life of people with subclinical coeliac disease by 2.44% or more (base-case value 1.48%; Figure 44).

Probabilistic sensitivity analysis

The results of probabilistic sensitivity analysis are shown in Figure 45 (CEAC) and Figure 46 (CEAF). These two graphs have very similar features to those seen in the PSA for case-finding in adult first-degree relatives; for an explanation and discussion, see p. 52.

The CEAF indicates that no testing should be considered the optimal option at cost-per-QALY thresholds below £29,000. At this level and above, maximal expected value is achieved with 1 of the testing strategies. Relatedly, the threshold at which some form of case-finding has the highest probability of being best-value option is approximately £30,000 per QALY.

Table 22: Base-case cost–utility results – case-finding in autoimmune thyroid disease (children)

Name	Absolute		Incremental			Net Monetary Benefit	
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)	£20K/QALY	£30K/QALY
NoTest	£10,329	24.0892				£471,455	£712,347
IgGDGP+IgAEMA+IgATTG	£10,433	24.0925	£104	0.0033	ext. dom.	£471,417	£712,343
IgGDGP+IgADGP+IgAEMA	£10,449	24.0934	£120	0.0042	£28,304	£471,420	£712,354
IgGDGP+IgADGP+IgAEMA+IgATTG	£10,457	24.0932	£8	-0.0003	dominated	£471,406	£712,338
IgGDGP+IgAEMA	£10,459	24.0933	£10	-0.0001	dominated	£471,406	£712,339
IgGDGP+IgATTG	£10,465	24.0938	£16	0.0004	£37,934	£471,412	£712,351
IgGDGP+IgADGP+IgATTG	£10,482	24.0933	£18	-0.0006	dominated	£471,384	£712,316
IgADGP	£10,538	24.0935	£73	-0.0004	dominated	£471,332	£712,267
IgATTG	£10,552	24.0943	£88	0.0005	ext. dom.	£471,335	£712,278
IgATTG+IgAEMA+HLA	£10,558	24.0948	£93	0.0009	£98,538	£471,338	£712,286
IgGDGP	£10,588	24.0938	£30	-0.0010	dominated	£471,289	£712,227
IgAEMA	£10,631	24.0942	£74	-0.0006	dominated	£471,252	£712,193
HLA	£10,753	24.0941	£196	-0.0007	dominated	£471,128	£712,069

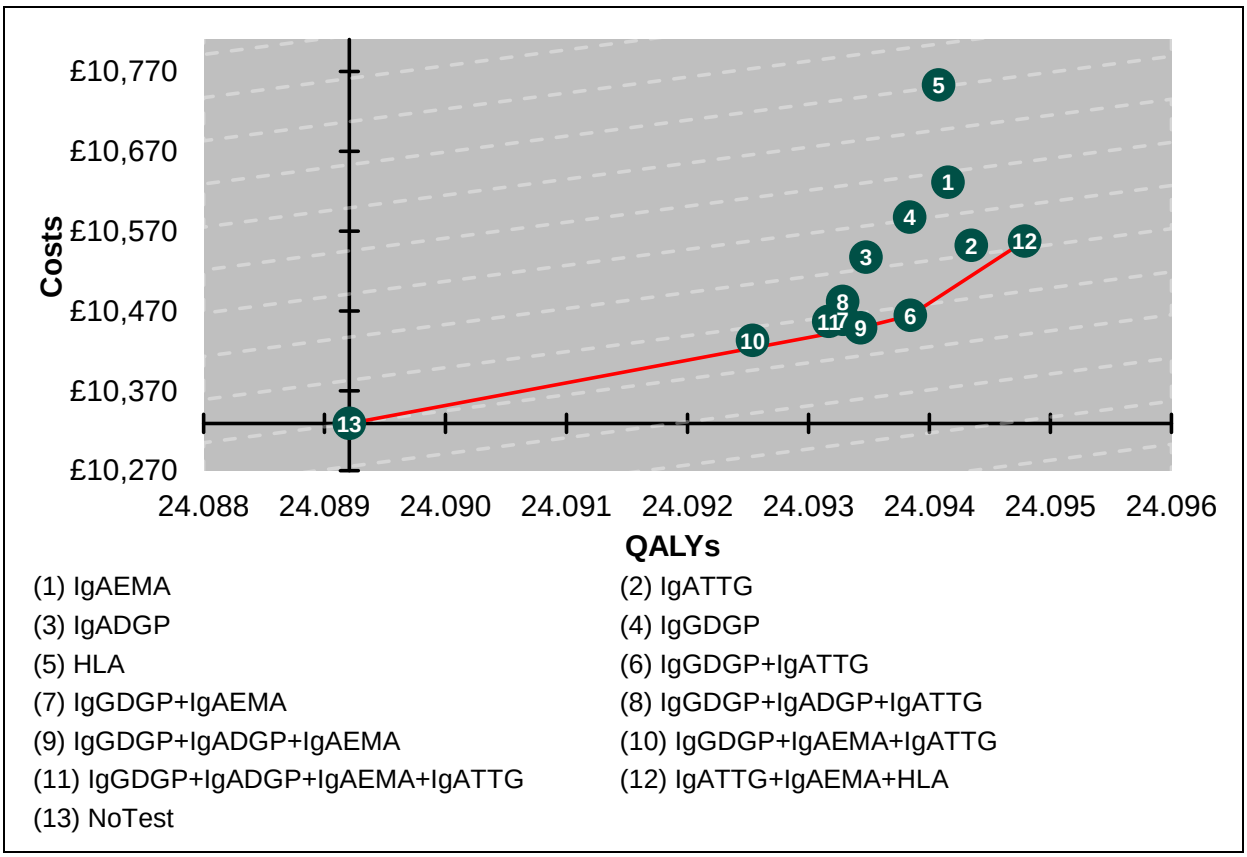
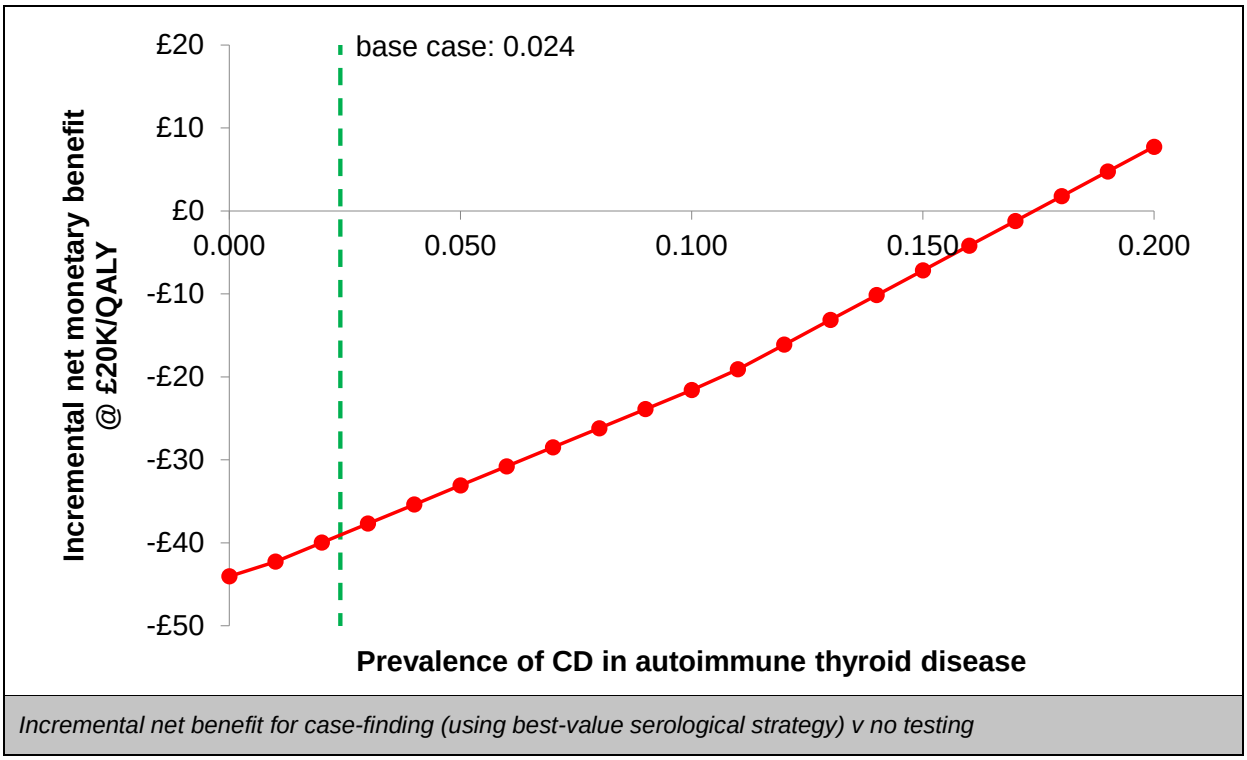
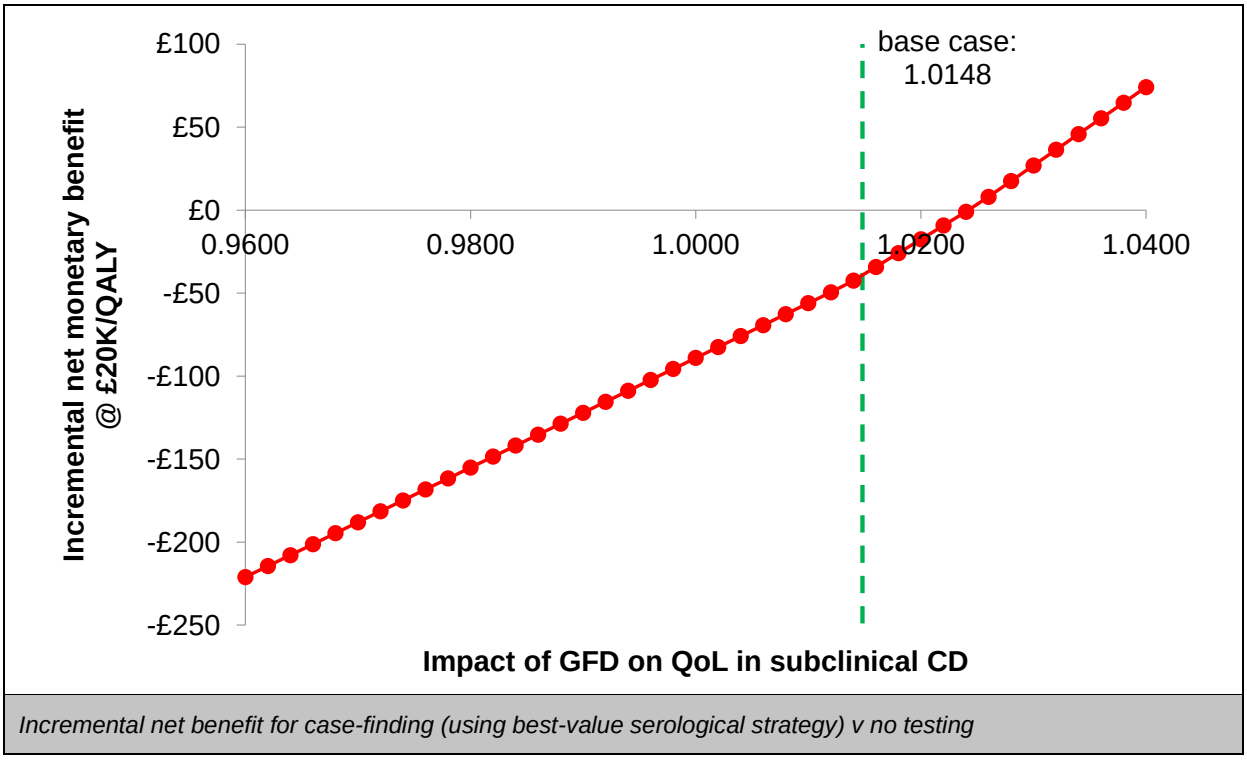


Figure 42: Base-case cost–utility plane – case-finding in autoimmune thyroid disease (children)



Incremental net benefit for case-finding (using best-value serological strategy) v no testing

Figure 43: One-way sensitivity analysis – case-finding in autoimmune thyroid disease – prevalence of coeliac disease (children)



Incremental net benefit for case-finding (using best-value serological strategy) v no testing

Figure 44: One-way sensitivity analysis – case-finding in autoimmune thyroid disease – impact of GFD on quality of life of people who have been diagnosed with subclinical coeliac disease (children)

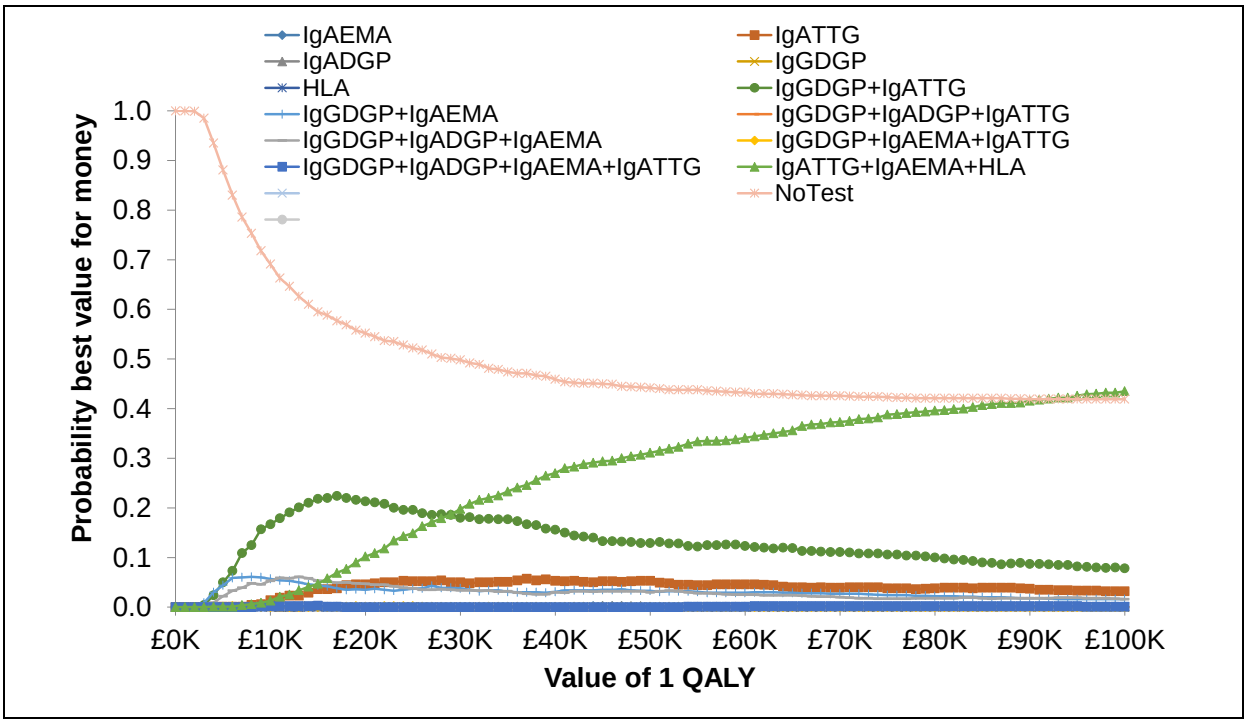


Figure 45: Probabilistic sensitivity analysis – cost-effectiveness acceptability curve: case-finding in autoimmune thyroid disease (children)

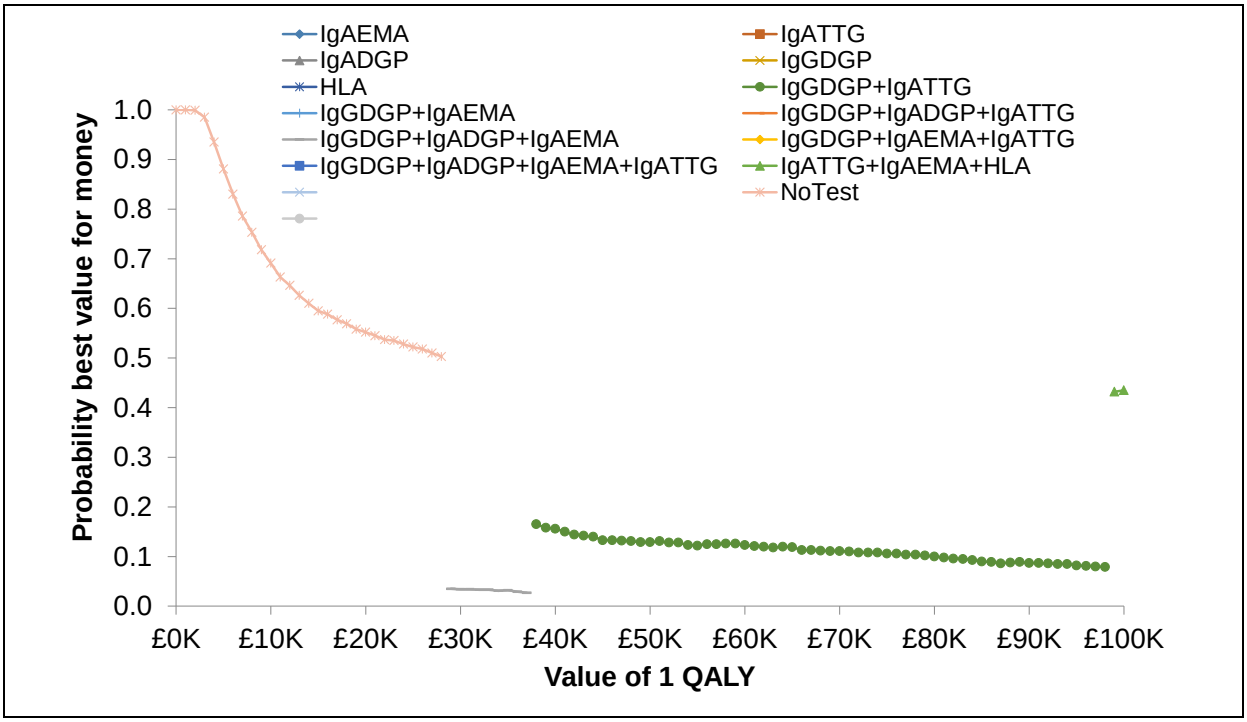


Figure 46: Probabilistic sensitivity analysis – cost-effectiveness acceptability frontier: case-finding in autoimmune thyroid disease (children)

G.2.4.7 Irritable bowel syndrome – adults

Base-case cost–utility results

Base-case incremental cost–utility results are tabulated in Table 23 and depicted on the cost–utility plane in Figure 47.

As with other case-finding populations, all testing strategies result in improved quality of life at increased cost compared with no testing, and the choice of optimal serological strategy closely mirrors that in the symptomatic diagnosis question (see G.1.4.2). The most sensitive strategies (IgA tTG alone and EitherIgATTG+IgAEMA [that is, considering people serologically positive if they are positive on either IgA tTG or IgA EMA]) produce greatest health gains, but the incremental benefits are small and come at substantial incremental cost, when compared with the recommended strategy in symptomatic people (that is, one that tests IgA tTG in all people and reserves IgA EMA to classify cases in which IgA tTG results are weakly positive). This approach has an ICER of £20,800 per QALY gained compared with no testing.

Deterministic sensitivity analyses

One-way sensitivity analyses exploring the model's sensitivity to key parameters are illustrated below.

Case-finding can be assumed to produce health at a cost of less than £20,000 per QALY if the prevalence of coeliac disease in the tested population exceeds 10% (base-case value 4.3%; Figure 48).

The ICER falls below £20,000 if it can be assumed that a gluten-free diet improves the health-related quality of life of people with subclinical coeliac disease by 1.64% or more (base-case value 1.48%; Figure 49).

These results are somewhat inconsistent with base-case findings, as they suggest relatively large changes to parameter values would be required to reduce the ICER to below £20,000 per QALY, when the base-case estimate is very close to that number. This is because of nonlinearity in the model leading to differences between deterministic and probabilistic outputs (see p. 61 for a discussion).

Probabilistic sensitivity analysis

The results of probabilistic sensitivity analysis are shown in Figure 50 (CEAC) and Figure 51 (CEAF). These two graphs have very similar features to those seen in the PSA for case-finding in adult first-degree relatives; for an explanation and discussion, see p. 52.

The CEAF indicates that no testing should be considered the optimal option at cost-per-QALY thresholds below £21,000. At this level and above, maximal expected value is achieved with 1 of the testing strategies. Relatedly, the threshold at which some form of case-finding has the highest probability of being best-value option is also approximately £21,000 per QALY.

Table 23: Base-case cost–utility results – case-finding in irritable bowel syndrome (adults)

Name	Absolute		Incremental			Net Monetary Benefit	
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)	£20K/QALY	£30K/QALY
NoTest	£9,702	19.7016				£502,539	£581,346
IgGDGP+IgADGP+IgAEMA	£9,820	19.7061	£118	0.0045	ext. dom.	£502,538	£581,363
IgGDGP+IgADGP+IgAEMA+IgATTG	£9,829	19.7060	£127	0.0044	dominated	£502,527	£581,351
IgGDGP+IgAEMA+IgATTG	£9,838	19.7071	£136	0.0055	ext. dom.	£502,545	£581,374
StepIgATTG_equiv_then_IgAEMA	£9,841	19.7083	£139	0.0067	£20,792	£502,574	£581,407
IgAEMA	£9,841	19.7081	£0	-0.0002	dominated	£502,570	£581,403
IgGDGP+IgATTG	£9,845	19.7070	£4	-0.0012	dominated	£502,538	£581,366
IgGDGP+IgADGP+IgATTG	£9,845	19.7072	£4	-0.0011	dominated	£502,542	£581,371
IgGDGP	£9,846	19.7079	£5	-0.0004	dominated	£502,558	£581,389
BothIgATTG+IgAEMA	£9,848	19.7081	£7	-0.0002	dominated	£502,562	£581,394
IgGDGP+IgAEMA	£9,848	19.7071	£8	-0.0011	dominated	£502,537	£581,366
StepIgATTG_then_IgAEMA	£9,851	19.7081	£10	-0.0001	dominated	£502,561	£581,393
IgATTG	£9,882	19.7084	£42	0.0001	£391,364	£502,535	£581,369
EitherIgATTG+IgAEMA	£9,897	19.7084	£15	0.0000	£520,057	£502,522	£581,355
IgADGP	£9,918	19.7075	£21	-0.0009	dominated	£502,477	£581,306

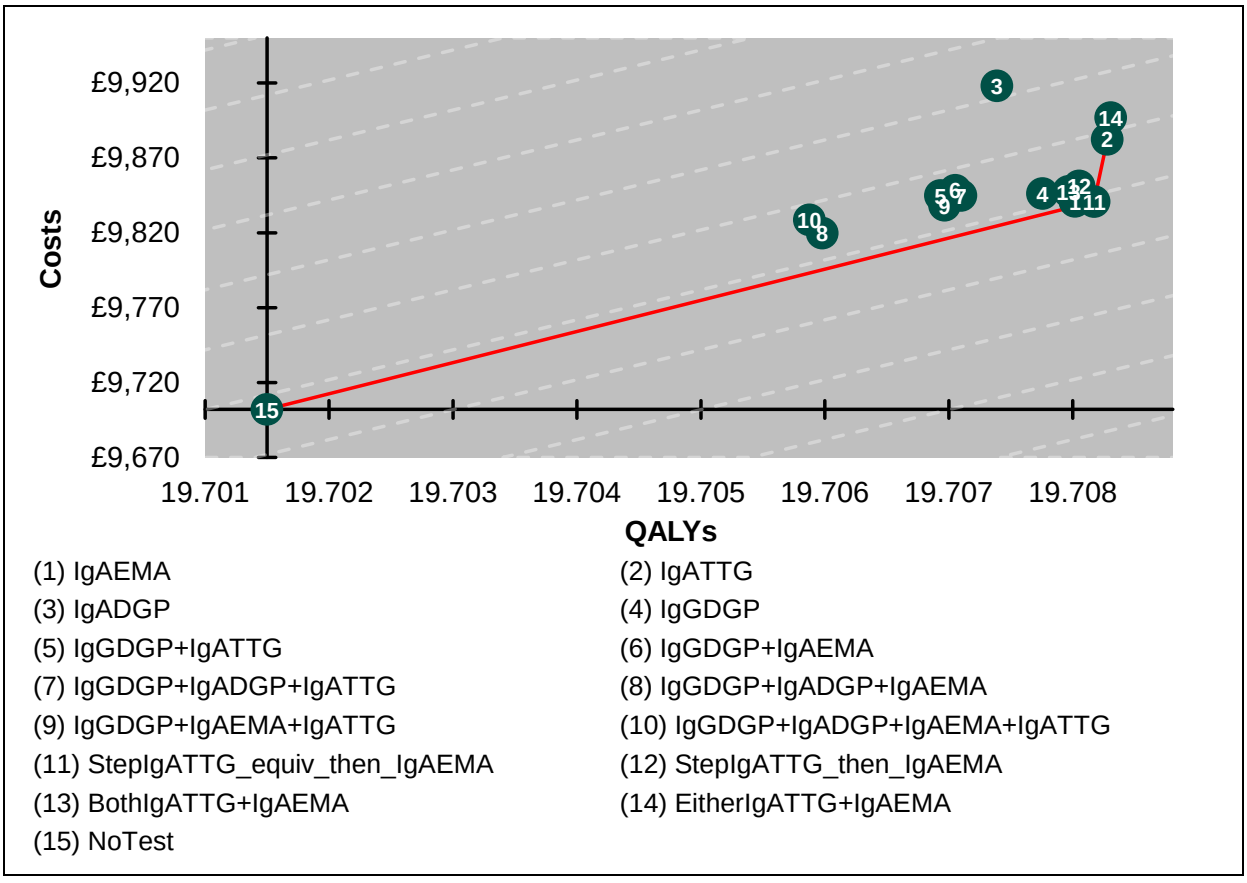
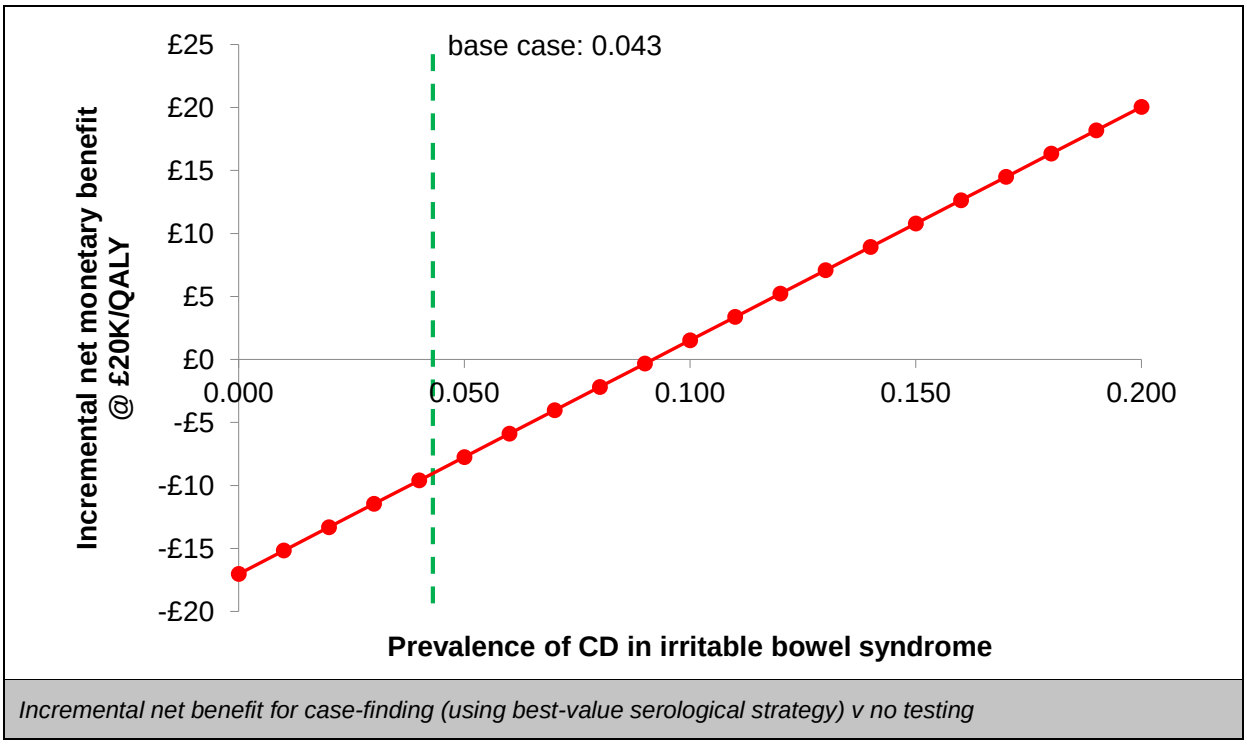
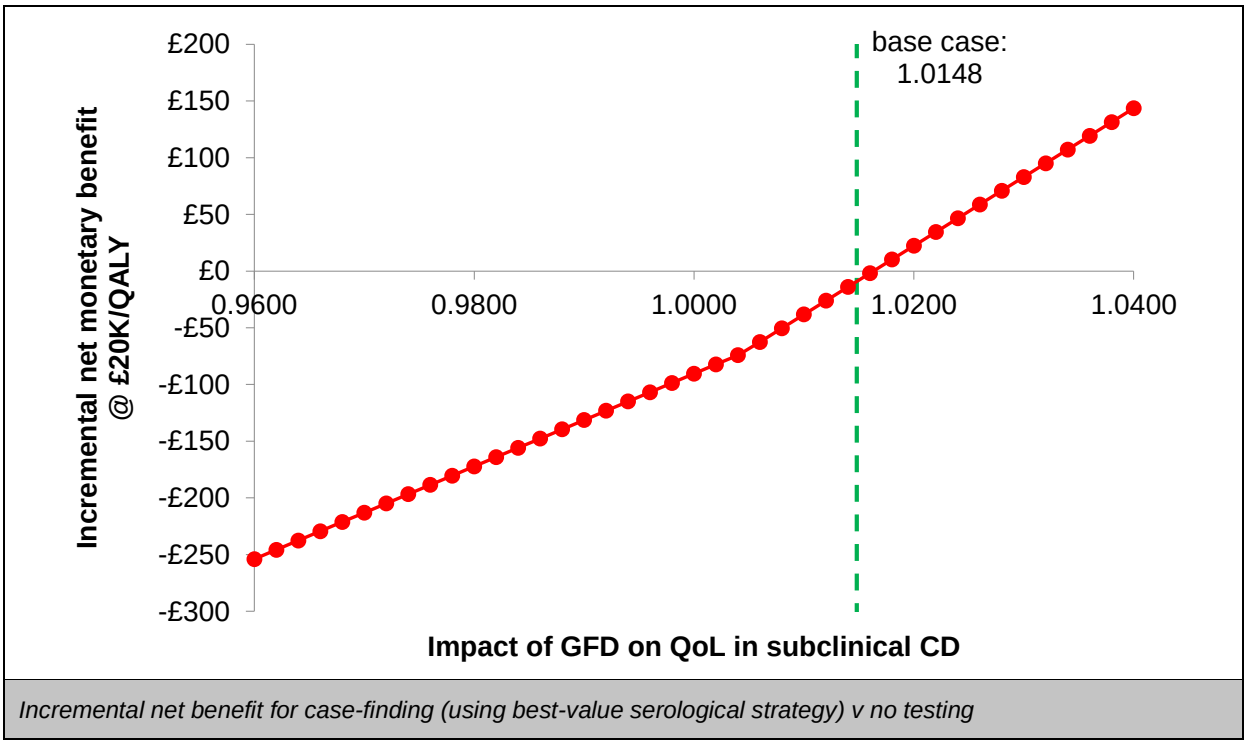


Figure 47: Base-case cost–utility plane – case-finding in irritable bowel syndrome (adults)



Incremental net benefit for case-finding (using best-value serological strategy) v no testing

Figure 48: One-way sensitivity analysis – case-finding in irritable bowel syndrome – prevalence of coeliac disease (adults)



Incremental net benefit for case-finding (using best-value serological strategy) v no testing

Figure 49: One-way sensitivity analysis – case-finding in irritable bowel syndrome – impact of GFD on quality of life of people who have been diagnosed with subclinical coeliac disease (adults)

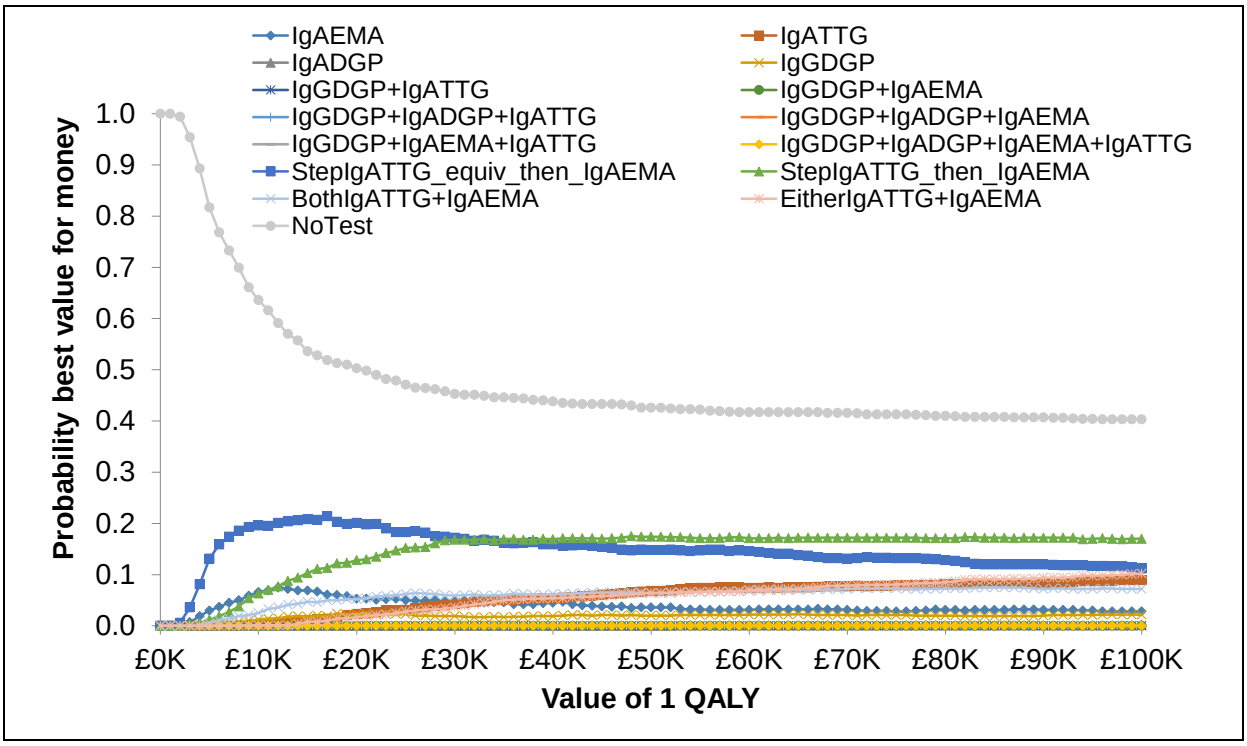


Figure 50: Probabilistic sensitivity analysis – cost-effectiveness acceptability curve: case-finding in irritable bowel syndrome (adults)

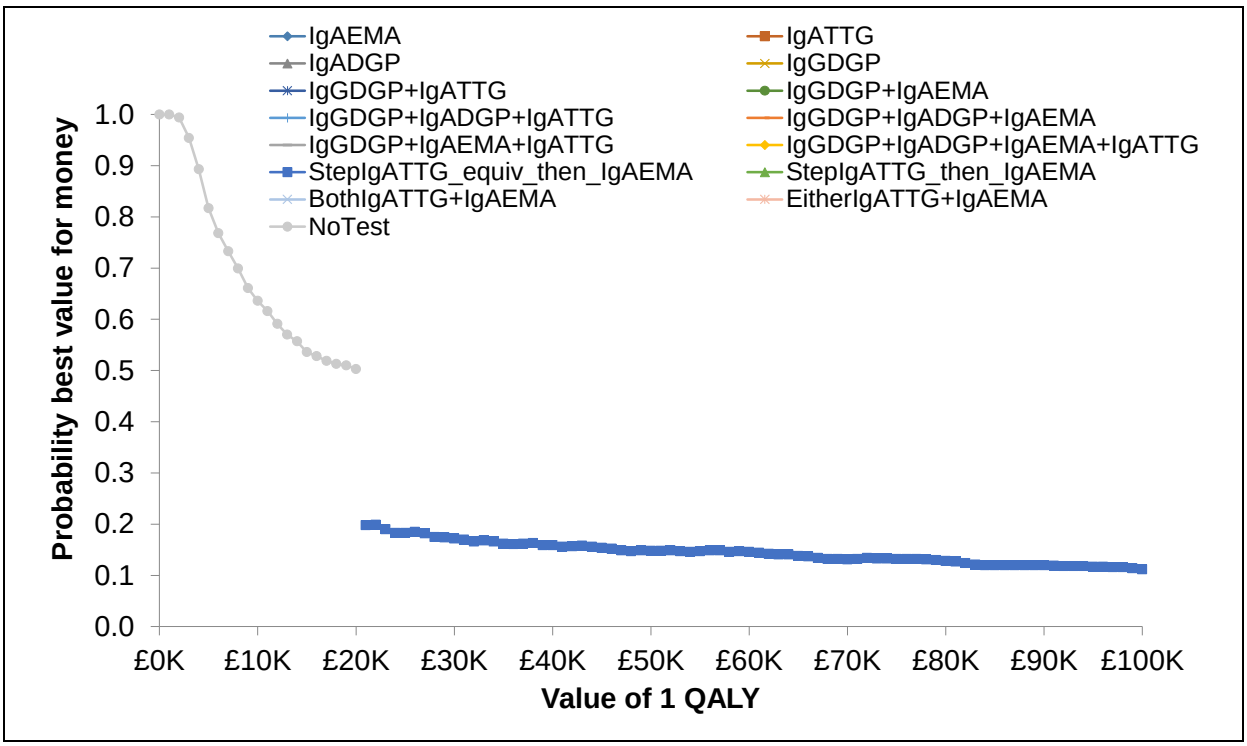


Figure 51: Probabilistic sensitivity analysis – cost-effectiveness acceptability frontier: case-finding in irritable bowel syndrome (adults)

G.2.5 Discussion

G.2.5.1 Principal findings

In all instances, we can be confident that case-finding results in an average health gain across the modelled cohorts. Whether this gain justifies the additional cost that is necessary to produce it is more ambiguous. The deterministic base-case ICERs for the best serological diagnostic strategy in each population range between £16,000 and £27,000 per QALY, compared with no screening. Probabilistic results suggested that maximal expected value is associated with case-finding strategies above cost-per-QALY thresholds of £18,000 to £27,000.

Conspicuously, the cost effectiveness of case-finding in all modelled populations was critically dependent on the parameter specifying the extent to which – if at all – a gluten-free diet improves the health-related quality of life of people with subclinical coeliac disease. Clearly, if identifying subclinical coeliac disease does not result in improvement in people's day-to-day quality of life, it is unlikely to be considered worthwhile.

G.2.5.2 Strengths of the analyses

All the strengths of our analysis for symptomatic diagnosis (see G.1.5.2) also apply here.

The GDG considered it a strength of the approach adopted that it treated the coexisting conditions and characteristics as concurrent with coeliac disease (that is, coeliac disease is not a differential diagnosis for people who have been erroneously diagnosed with the condition in question). The group thought this was particularly important for IBS, in which coeliac disease has previously been modelled as a differential diagnosis (e.g. Mohseninejad et al., 2013).

G.2.5.3 Weaknesses of the analyses

These analyses also inherit the weaknesses of our model for symptomatic diagnosis (see G.1.5.3).

In addition, it is a potential limitation of our analysis is that we were unable to identify evidence quantifying the diagnostic accuracy of various serological testing strategies in the particular populations being simulated. The sensitivity and specificity of tests are usually believed to be relatively invariant to the population in which testing is undertaken. However, there may be instances, here, where such an assumption may be misleading. One key example is in the specificity of HLA DQ2/DQ8 in first-degree relatives of people with a diagnosis of coeliac disease. The GDG pointed out that, if one family member is HLA DQ2/DQ8 positive (as the index case almost certainly would be), the chances of the rest of that family being HLA DQ2/DQ8 positive is very high. Therefore, the utility of doing that test in relatives is negligible, as its specificity will be close to 0. This shows that there are some areas in which population-specific diagnostic accuracy data might improve the accuracy of results.

It is possible that our model underestimates health gain associated with diagnosis of coeliac disease as it only focuses on quality of life implications of diagnosis and management of coeliac disease. The GDG believed that, in some circumstances, correct identification of coeliac disease would also lead to superior management of the underlying condition, with associated improvement in quality of life. In the case of type 1 diabetes, the glycaemic control of people with subclinical CD is known to be improved by adopting a GFD. Additionally, dietary management is complex in people with both conditions, as each imposes its own requirements; in this context, access to appropriate dietetic support is critical, so diagnosis of subclinical coeliac disease is very important. In the case of

autoimmune thyroid disease, untreated coeliac enteropathy may interfere with the absorption of oral medications that are critical to managing the condition. Correct identification of coeliac disease, therefore, should be associated with more stable and effective medication requirements, improving the person's quality of life. In both these instances, it would be very hard to quantify the additional benefits; however, it is noted that they are missing from our analysis, which would tend to bias our cost-effectiveness estimates upwards.

As noted above, model outputs are critically dependent on the parameter specifying the extent to which – if at all – a gluten-free diet improves the health-related quality of life of people with subclinical coeliac disease. The evidence on which this parameter is based is very uncertain, although it accorded well with the GDG's experience and beliefs. Nevertheless, it is entirely possible that more authoritative evidence on this parameter would alter model conclusions substantially.

G.2.5.4 Conclusions

Active case-finding in people with characteristics and/or coexisting conditions that put them at increased risk of coeliac disease appears to improve the average quality-adjusted life expectancy of the cohort. These gains come at incremental costs that tend to be close to conventional thresholds for effective use of NHS resources.

The most plausible ICER for case-finding, compared with no testing, is below £20,000 per QALY for first-degree relatives of people with coeliac disease (adults and children) and adults with type 1 diabetes. For children with type 1 diabetes, adults and children with autoimmune thyroid disease and adults with irritable bowel syndrome, the most plausible ICER is in the range £20–30,000 per QALY; however, as it focuses on coeliac disease alone, our model may not fully reflect the total benefit of accurate diagnosis in these populations.

G.3 Dietitian-led follow-up of people with coeliac disease (full guideline section 5.4)

G.3.1 Original cost–utility model – methods

G.3.1.1 Overview of the model

Table 24: Modelled population(s) and intervention(s)

Populations	Adults with a diagnosis of coeliac disease
Intervention	Dietitian-led follow-up, including consultation with a dietitian, routine blood tests, DEXA scan and possible gastroenterology review
Comparator	Usual care
Outcomes	Cost–utility analysis based on the benefits and harms (estimated in quality-adjusted life years[QALYs]) and costs of diagnosing coeliac disease.

The economic model for this question is based on the one used for the diagnostic question in people with symptoms of coeliac disease. Details of model structure and common parameters are provided in section G.1.3, above.

The initial decision-tree structure of the diagnosis model was not required, for this question: the entire modelled population has a true-positive diagnosis of coeliac disease.

The model features only 1 effectiveness parameter; this sought to capture the extent to which dietitian-led follow-up can be expected to improve adherence to GFD. We drew this value from a very low-quality study (Wylie et al., 2005); for this reason, as well as the speculative nature of the model structure, we consider this analysis exploratory.

G.3.1.2 Additional parameters

See section G.1.3.2 for details of our general approach to identifying and selecting model parameters.

Only 1 additional effectiveness parameter was required for this model: the extent to which dietitian-led follow-up can be expected to improve adherence to GFD. This was calculated on a log-odds scale, and then converted to probabilities for use in the model; this is a convenient way of constraining probabilities to their required [0,1] range.

The costs of the monitoring strategy are estimated by allocating unit costs to the resource use described in the Wylie et al. (2005) paper. There was a lack of availability of unit costs to allocate to the dietitian consultation and the routine blood tests therefore appropriate proxies were sourced and their use agreed by the GDG. Costs associated with the resource use are sourced from NHS Reference Costs (2012–13). The model assumes that a DEXA scan takes place at the first appointment but is not conducted annually.

We only modelled an adult population, for this question. The study from which effectiveness data were drawn did not include any children, and results may not generalise to the paediatric population.

The model maintains an NHS and PSS perspective and excludes any privately borne costs such as any gluten-free products not provided on prescription.

Table 25: Additional parameter required for dietitian-led follow-up model

Parameter	Value (95%CI)	Distribution and parameters	Source
Effectiveness of intervention			
Probability of adherence to GFD			
Before dietitian-led follow-up	0.545		Wylie et al. (2005)
After dietitian-led follow-up	0.657		
Ln(OR) after -v- before	0.466 (-0.108, 1.039)	Normal: μ=0.466; σ=0.292	
Costs of intervention			
Senior dietitian appointment	£35.00		PSSRU 2013
Routine blood tests	£10.83		CG86 estimate inflated to 2012/13 prices
DEXA scan	£67.03		NHS Reference Costs
Gastroenterology review (adults)	£170.85		
Gastroenterology review (children)	£276.47		
% requiring gastroenterology review	25% (6%, 44%)	Triangular: min=0%; mode=25%; max=50%	
Total intervention costs (first year)	£155.57		
Total intervention costs (subsequent years)	£88.54		

G.3.2 Results

G.3.2.1 Cost–utility results

Base-case cost–utility results

Base-case incremental cost–utility results are tabulated in Table 26. The model estimates that, compared with usual care, dietitian-led follow-up results in average gains of approximately one-sixth of a QALY per person, at a cost of around £2500, leading to an ICER of £15,600 per QALY gained.

Table 26: Base-case cost–utility results – dietitian-led follow-up

	Absolute		Incremental			Net Monetary Benefit	
Name	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)	£20K/QALY	£30K/QALY
Usual care	£15,895	14.8618				£281,341	£429,959
Dietitian-led follow-up	£18,388	15.0218	£2,493	0.160	£15,576	£282,049	£432,267

Deterministic sensitivity analyses

Figure 52 shows a 1-way sensitivity analysis exploring the relationship between the effectiveness parameter (improvement in adherence to GFD) and modelled cost effectiveness. Note that, although the effect is parameterised on a log-odds scale in the model, the log-odds ratios have been converted to equivalent risk ratios on a natural scale for ease of interpretation, here. This analysis suggests that the adoption of a dietitian-led follow-up protocol is likely to generated health at a cost of less than £20,000 per QALY if it can be assumed that adherence to GFD is improved by 15% or more.

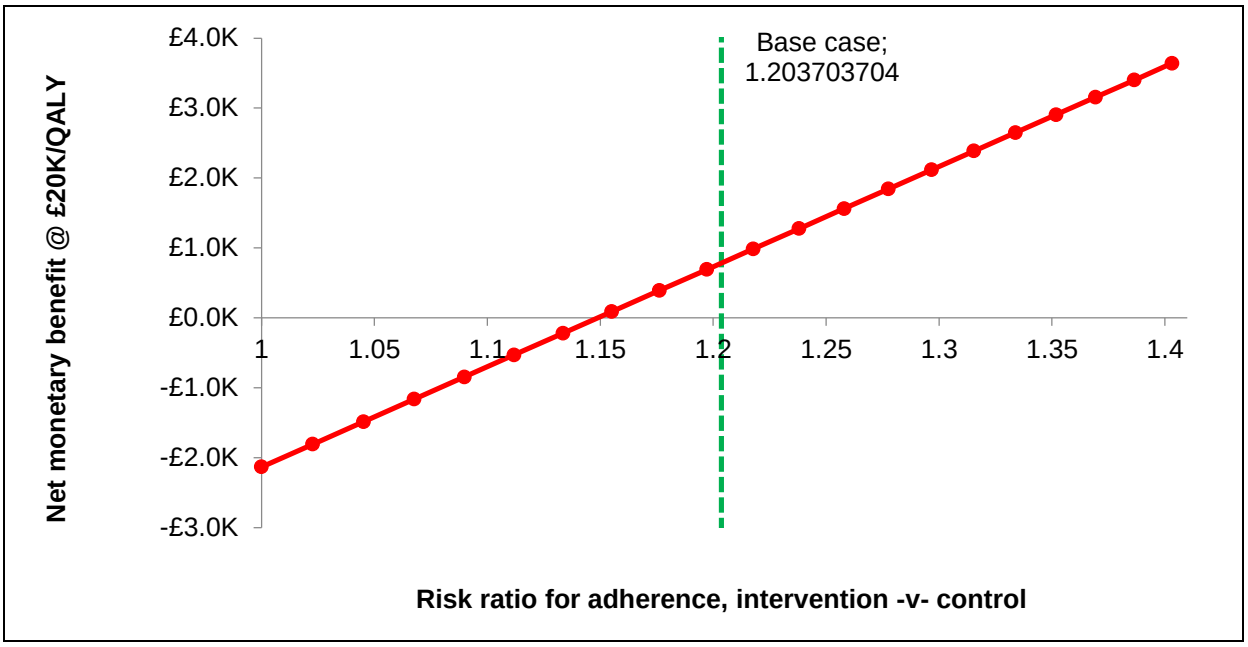


Figure 52: One-way sensitivity analysis – dietitian-led follow-up – risk ratio for adherence

Probabilistic sensitivity analysis

Results of the PSA are shown in Figure 53 (CEAC) and Figure 54 (CEAF). This suggests that the probability that dietitian-led follow-up provides best value for money is 65%, if QALYs are assumed to be valued at £20,000 each.

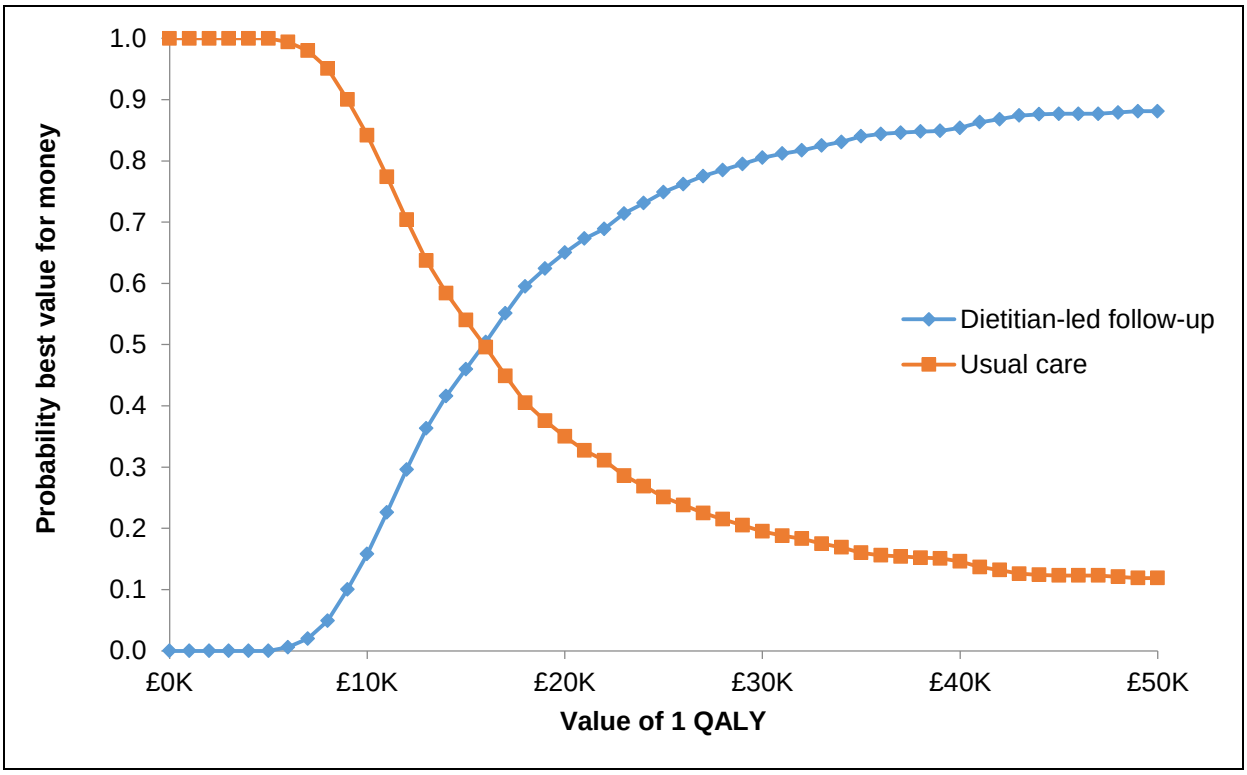


Figure 53: Probabilistic sensitivity analysis – cost-effectiveness acceptability curve: dietitian-led follow-up)

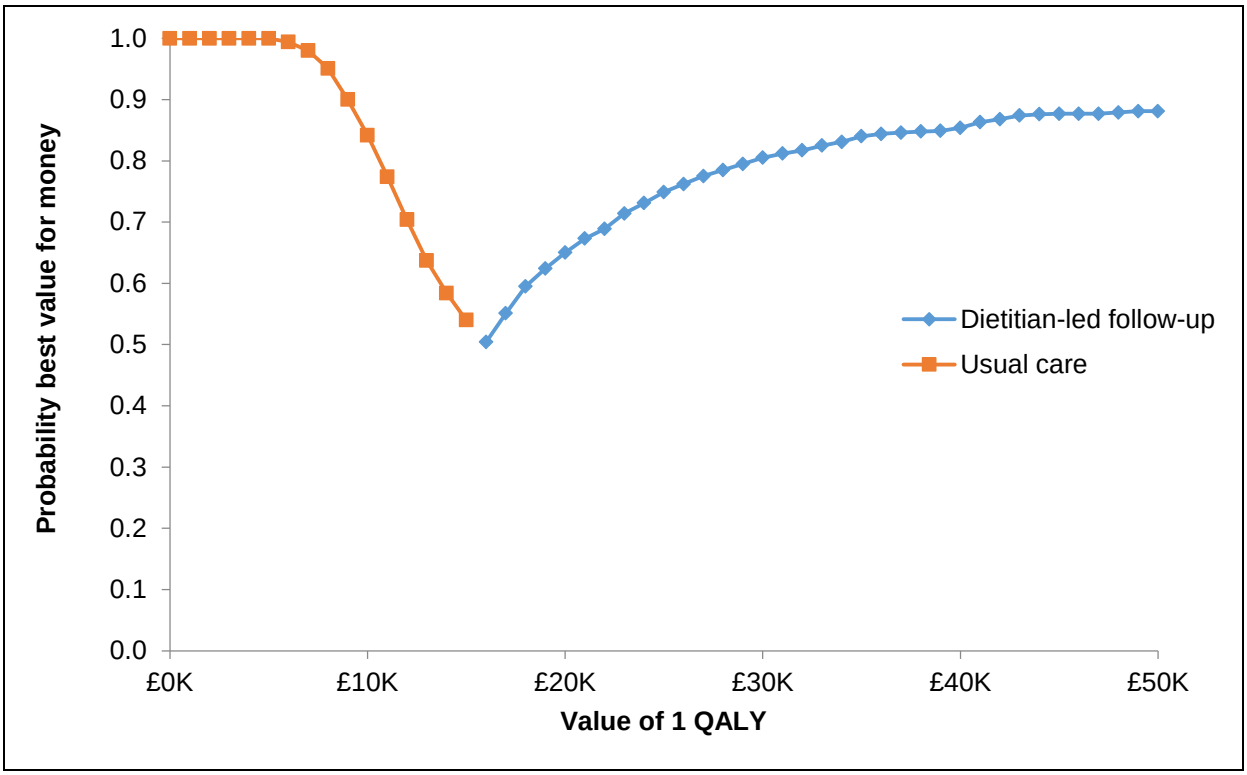


Figure 54: Probabilistic sensitivity analysis – cost-effectiveness acceptability frontier: dietitian-led follow-up

G.3.3 Discussion

The original health economic modelling undertaken for this question was exploratory in nature, and totally reliant on a single parameter from a very low-quality before-and-after study (Wylie et al., 2005) to estimate the effectiveness of dietitian-led follow-up (in terms of improved adherence to GFD). The package of follow-up care reported in this study comprised multiple elements, including dietetic review, DEXA scanning, blood tests and gastroenterological referral for a proportion of patients. It was not possible to identify what contribution each of these components made to the reported effect. However, when it came to the outcome that was critical to the health economic model – adherence to GFD – the GDG was content to assume that the involvement of a dietitian was the critical factor.

Therefore, if the improvement in adherence to GFD reported by Wylie et al. (2005) can be believed, our model suggests that dietitian-led follow-up is very likely to be a cost-effective strategy. However, the shortcomings of this evidence make it difficult to be confident of the size of effect that would be seen in practice.

G.4 References

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