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Comparative cost-effectiveness of three post-radiofrequency ablation surveillance intervals for Barrett's esophagus

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ABSTRACT

Background and study aims Radiofrequency ablation (RFA) for dysplastic Barrett's esophagus (BE) has resulted in a paradigm shift in the management of BE. Despite widespread adoption of RFA, the optimal surveillance interval of the ablated zone is unclear.

Methods A patient-level discrete time cycle Markov model was developed to model clinical surveillance strategies post-RFA for BE. Three surveillance strategies were examined: the American College of Gastroenterology (ACG) strategy based on ACG guidelines for post-RFA surveillance, the Cotton strategy based on data from the USA and UK RFA registries, and the UK strategy in line with surveillance strategies in UK centers. Monte-Carlo deterministic and probabilistic analyses were performed over 10,000 iterations (i. e., representing 10,000 patient journeys) and sensitivity analyses were carried out on the variables used in the model.

Results On base-case analysis, the ACG strategy was the most cost-effective strategy, at a mean cost of £ 11,733 ($ 16,396) (standard deviation (SD) 1520.15) and a mean effectiveness of 12.86 (SD 0.07) QALYs. Probabilistic sensitivity analysis demonstrated that the ACG model was the most cost-effective strategy with a net monetary benefit (NMB) of £ 5,136 ($ 7177) (SD 241) compared to the UK strategy and a NMB of £ 7017 ($ 9,806) (SD 379) compared to the Cotton strategy. At a willingness to pay (WTP) threshold of £ 20,000 ($ 27,949), the ACG model was superior to the other strategies as the most cost-effective strategy.

Conclusions A post-RFA surveillance strategy based on the ACG guidelines seems to be the most cost-effective surveillance option.

Introduction

The management of dysplastic Barrett's esophagus (BE) has evolved over the last decade. Dysplasia in BE increases the risk of esophageal adenocarcinoma (EAC) [1, 2]. A systematic review examining the factors associated with progression of BE determined that older age, male sex, longer BE segment, and low-grade dysplasia (LGD) was associated with progression to high-grade dysplasia (HGD) or EAC and suggested intensive endoscopic surveillance for these groups [3]. The risk of progression of BE-indefinite for dysplasia was also noted to be similar to the risk of LGD [4]. Treatment of dysplasia is therefore critical in preventing progression to EAC.

Endoscopic resection of visible lesions with ablative treatment of flat dysplasia and residual non-dysplastic BE with radiofrequency ablation (RFA) has become the standard of care [5–

13]. Successful RFA is achieved by complete remission of intestinal metaplasia (CRIM) both endoscopically and at histological analysis. Despite CRIM, there is evidence to suggest that there is recurrence of both intestinal metaplasia (IM) and dysplasia of up to 9.5 % for IM and 2 % to 3 % for dysplastic recurrences annually [14–16]. Recurrence of IM can occur after 2 to 3 years, with most recurrences being non-dysplastic [17–19]. Dysplastic recurrences, including EAC, may occur in up to 25 % of cohorts [17, 20].

Endoscopic surveillance, therefore, is necessary to detect and treat recurrent dysplasia and prevent progression to esophageal adenocarcinoma (EAC).

There is no clear consensus as to the optimal post-RFA surveillance strategy, given limited evidence. The American College of Gastroenterology (ACG) guidelines for post-RFA follow-up suggest 6-monthly surveillance for the first year if pre-RFA histology was LGD followed by annual surveillance, and 3, 6, 9 and 12 monthly follow-up in the first year, 6 monthly in the second year, followed by annual surveillance for pre-RFA HGD [19].

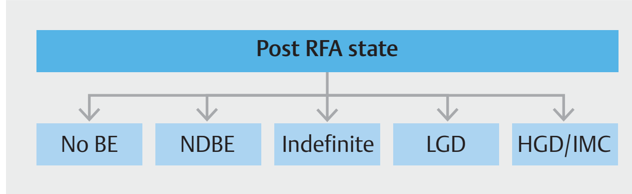
Other centers, including many in the United Kingdom (UK), follow a strategy of endoscopic surveillance at 3, 6, and 12 months in the first year after achievement of CRIM, irrespective of pre-RFA histology, followed by annual surveillance.

Based on data from the US and the UK RFA registries, Cotton, et al [21] suggested 1 and 3 yearly surveillance frequencies if the pre-RFA histology was LGD and 3, 6, and 12 monthly surveillance initially for pre-RFA HGD followed by annual surveillance. In their dataset, yield of surveillance for pre-RFA non-dysplastic BE or histology "indefinite for dysplasia" was very low up to 7 years post-CRIM and the authors did not propose any surveillance intervals for these groups. An American College of Gastroenterology (AGA) 2020 update proposed surveillance strategies similar to the Cotton study [22].

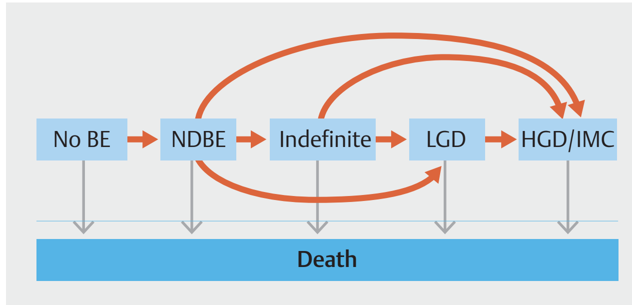
Due to the lack of comparative cost-effectiveness data between the current surveillance strategies, we sought to perform a decision analysis comparing strategies using a cost-effectiveness approach, in order to determine the optimal surveillance strategy.

Methods

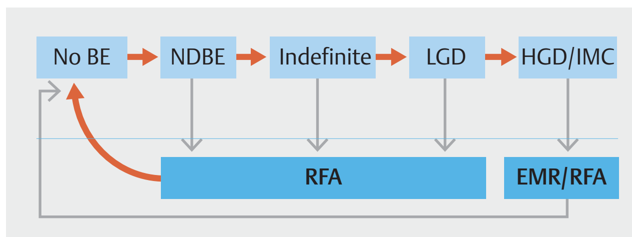
In a large multicenter international study, a cohort of 594 patients with BE underwent endoscopic resection of macroscopic and nodular dysplasia followed by RFA and underwent surveillance following CRIM [10]. Nearly 90 % of the cohort had dysplastic BE, of which nearly 66 % had HGD or intramucosal cancer (IMC). During follow up, dysplastic recurrences occurred in 31.1 %, of which 11.9 % were LGD, 7.9 % were HGD and 9.3 % were EAC, with the majority of cancers (85 %) being superficial (T1a or T1b) recurrences. The annual recurrence rate was 2.8 % for dysplastic recurrences and 1.6 % for HGD/EAC recurrences. Interestingly, pre-RFA baseline HGD/EAC histology was predictive of dysplastic (4.3 % annually, hazard ratio (HR) 4.81 (95 % confidence intervals (CI) 1.21–19.18, P = 0.026)) or HGD/EAC recurrence (2.3 % per year). Pre-RFA HGD/EAC histology was also associated with the risk of any recurrence (HR 1.95, 95 % CI 1.07–3.56, P = 0.029). The authors also found that the cumulative recurrence rates of non-dysplastic and dysplastic BE following CRIM did not appear to plateau over the first 5 to 6 years of follow-up, suggesting that surveillance over this period is reasonable. The analysis was conducted using a health system perspective, meaning broader societal costs were not included in the base case. This aligns with the approach recommended by the National Institute for Health and Care Excellence.



► **Fig. 1** Clinical progression of the transition states.



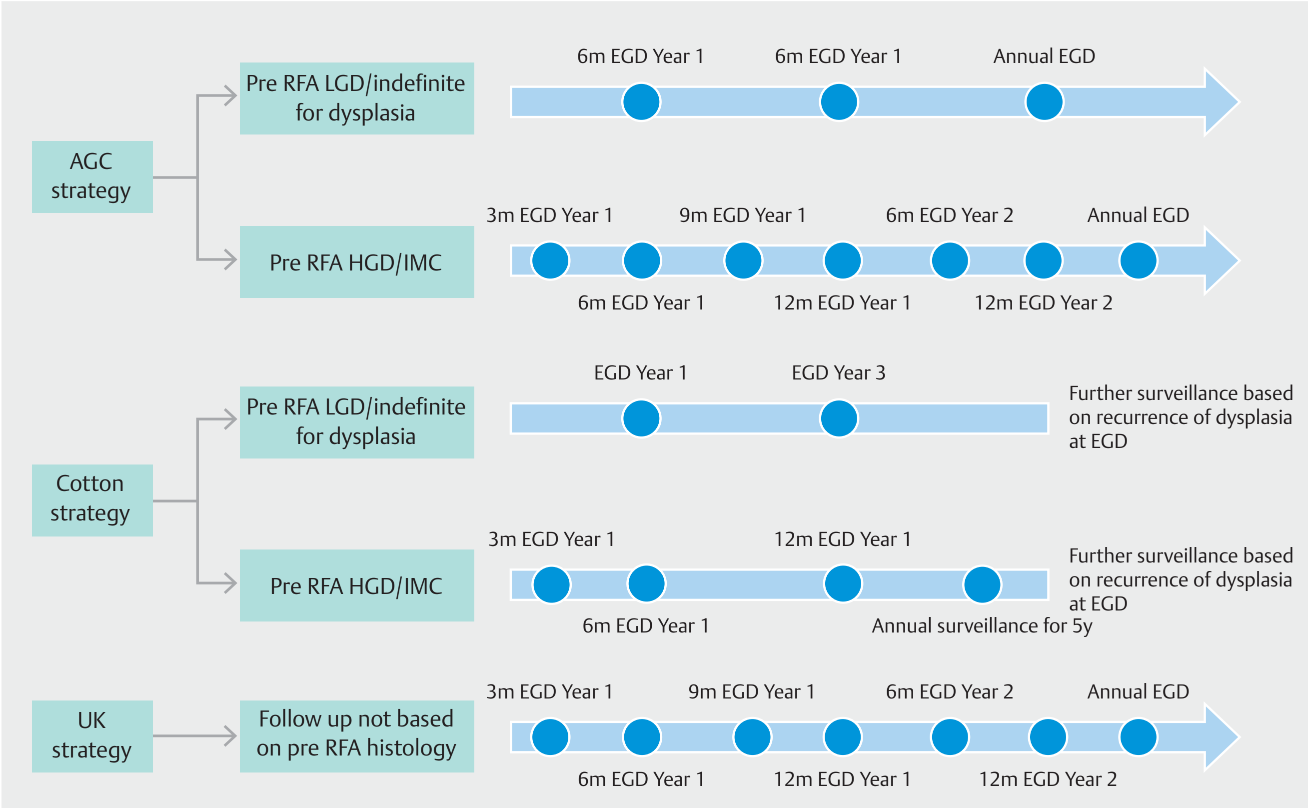
► **Fig. 2** Progression into other transition states.



► **Fig. 3** Treatment of dysplasia.

Health economic analyses

A decision analytic Markov state transition model was developed to compare the three surveillance strategies (► **Fig. 1**, ► **Fig. 2**, ► **Fig. 3**). The model examined a cohort of patients with dysplastic BE (LGD, HGD and IMC) having achieved CRIM, who were followed over a time horizon of 40 years. Patients entered the model at age 50 years and were followed up until reaching age 90 years. Healthcare states in the model included no BE recurrence, non-dysplastic BE, and dysplastic recurrence (indefinite for dysplasia, LGD, HGD/IMC). The Markov cycle length was 12 months between state transitions. Data to inform the initial construction of the model were adapted from a multicenter international cohort of patients following CRIM [10]. Analyses were performed using TreeAge Pro 2021 (TreeAge, Williamstown, Massachusetts, United States).



▶ **Fig. 4** Post CRIM strategies.

A base-case analysis was performed using point estimates for model parameters and transition probabilities. A microsimulation was performed over 10,000 runs to determine the effect of a range of variable estimates on results. Sensitivity analyses were undertaken to evaluate uncertainty regarding the input values and structural assumptions in the model. The Incremental Cost-Effectiveness Ratio (ICER) was determined by calculating the differences in the total cost and quality-adjusted life year (QALY) of the three strategies. Net monetary benefit (NMB) was calculated for each strategy with the willingness to pay (WTP) threshold set at £ 20,000, in keeping with the UK National Institute for Health and Care Excellence (NICE) recommendations for a WTP threshold of £ 20,000 to £ 30000 [23–25]. A probabilistic sensitivity analysis was performed over 10,000 iterations to examine the impact of uncertainty modeled as distributions. Cost-effectiveness data were calculated, and acceptability curves were evaluated for various WTP thresholds. Costs and utilities were discounted at an annual rate of 3 % (0 % to 5 % in sensitivity analysis).

Strategies used in the model

The three post CRIM surveillance strategies (▶ **Fig. 4**) were labeled as the ACG strategy, the UK strategy and the Cotton strategy (▶ **Table 1**).

ACG strategy

The ACG clinical guideline [19] suggested 3-monthly endoscopic follow up for pre-RFA HGD/IMC patients in the first year following CRIM, followed by every 6 months in the second year and annually thereafter. Patients' indefinite for dysplasia and LGD underwent endoscopic surveillance every 6 months in the first year and annually thereafter.

Cotton strategy

Cotton, et al [21] examined data from the United States and UK RFA registries [11, 26] and developed models to predict the risk of dysplasia following RFA for CRIM. They found that the risk of neoplastic recurrence was associated with the most severe pre-RFA histologic grade. They determined from their datasets that the yield of surveillance for patients with non-dysplastic BE or indefinite for dysplasia was very low and this risk remained as such for up to 7 years post CRIM. They suggested surveillance at 1 and 3 years post-CRIM for pre-RFA LGD and surveillance at 3 months, 6 months, 1 year and annually until 5 years post-CRIM for pre-RFA HGD/IMC. For pre-RFA non-dysplastic and indefinite for dysplasia cohorts, we modeled an index endoscopy at 12 months post CRIM, followed by 3-yearly surveillance.

UK strategy

In the previous strategies, pre-RFA histology was used to determine surveillance intervals. However, there is no consensus on this strategy and a separate model, which we have termed UK

▶ **Table 1** Comparison of the three strategies used in the model.

Pre-RFA histology	ACG strategy Post-RFA surveillance based on pre-RFA histology	Cotton strategy Post-RFA surveillance based on pre-RFA histology	UK strategy Post-RFA surveillance (irrespective of pre-RFA histology)
BE[1]			For post RFA BE: Surveillance EGD every 2 years
LGD[1]	6 monthly EGD	1, 3-year EGD	For post RFA-LGD: 6 monthly EGD
HGD/IMC	3 monthly EGD year 1 6 monthly EGD year 2 Annual EGD thereafter	3, 6, 12 monthly EGD year 1 Annual EGD thereafter	For post RFA-HGD: 3 monthly EGD year 1 6 monthly EGD year 2 Annual EGD thereafter

RFA, radiofrequency ablation; BE, Barrett's esophagus; LGD, low-grade dysplasia; HGD, high-grade dysplasia; IMC, intramucosal cancer; EGD, esophagogastroduodenoscopy.
[1] BE and LGD were treated by ablation and followed up as indicated if persistent.

model, suggests follow-up of all patients post-CRIM in a similar fashion, with treatment and separate follow-up if dysplasia develops during the follow-up period. In this surveillance strategy, all patients underwent 3-monthly endoscopic surveillance in the first year post-CRIM, 6-monthly surveillance in the second year and annual surveillance thereafter, irrespective of their pre-RFA histology. LGD recurrence was treated with RFA and followed up at 6 months and annually thereafter. HGD/IMC recurrence was treated and was followed up every 3 months for 6 months and annually subsequently.

Assessment during surveillance

At surveillance endoscopy in our strategies, we assumed that all patients would undergo high-quality white light endoscopy with detailed mucosal examination using mucolytics and quadrantic tissue acquisition at 2-cm vertical intervals in the tubular esophagus and separate biopsies taken from the gastroesophageal junction [19]. Histological costs were therefore not separately modeled. All patients were assumed to be on acid suppression with proton pump inhibitors (PPIs). Macroscopic HGD/IMC detected at surveillance was treated by endoscopic resection and residual BE was treated by subsequent ablation with RFA. Non-dysplastic BE and LGD detected at surveillance was also treated using RFA. Treatment of non-dysplastic post-RFA BE recurrence is controversial as there is debate as to whether recurrent IM is biologically similar to the original BE with a similar risk of EAC. A recent retrospective multicentre study of treated BE patients who had achieved CRIM reported recurrence of IM in 30 % of the cohort with an annual incidence rate of 9 % per year [27]. In this cohort, 47 % were observed and the rest were treated using ablative methods and interestingly, there was no difference in the rates of recurrent dysplasia between patients who underwent ablation compared to the group that underwent observation and another cohort who did not have any IM recurrence. We modeled ablation for recurrent BE in this study as the current evidence is not clear as to whether these patients can be simply observed.

Model assumptions

The model (▶ **Fig. 1**, ▶ **Fig. 2**, ▶ **Fig. 3**) examined a cohort of patients aged 50 years who were followed up until the age of 90 or death. We assumed that endoscopic therapy could be performed with low overall clinical risk to an advanced age and would be important and acceptable to patients. All-cause mortality was modeled using European age adjusted SMR [28]. Data on short (< 3 cm) and long segment (> 3 cm) BE was modeled from a prior international study [10]. Adverse events from endoscopic mucosal resection and RFA were incorporated into the model from a systematic review and meta-analysis [29]. Esophageal repair of perforation secondary to EMR and RFA were included in the model with mortality secondary to endoscopic/surgical morbidity modeled in. Although diagnostic gastroscopy can be associated with a perforation rate of 1 in 2500 to 1 in 11000 and a mortality risk of 1 in 10000 [30], for purposes of the model, we assumed that post-RFA surveillance and management were performed in centers of expertise with experienced endoscopists and, therefore, assumed that there would be no risk of causing esophageal perforation with a diagnostic gastroscopy. The ACG and UK strategies were compared against the Cotton strategy.

We also assumed that all HGD/IMC detected at surveillance was endoscopically treatable. We did not model endoscopically non-resectable HGD/IMC or advanced esophageal cancer owing to the lack of paucity of data pertaining to non-endoscopically resectable HGD/IMC in the post-RFA setting in the literature, as it would have led to significant uncertainty in projections. Annual recurrence rates for dysplasia following CRIM were similar in all three strategies.

Costs and resource use

Average PPI costs based on UK NHS (National Health Service) tariffs were adjusted into the model [31]. Unit costs for healthcare interventions were based on the NHS national payment tariffs for 2019 and 2020 [32].

Variables and estimates used in the model inputs

A literature search was performed to identify and inform model estimates [4, 10, 19, 31, 33–35]. Healthcare utilities (HRQoL) were derived from published literature (▶ **Table 1**). HRQoL is measured on a scale needed for the conduct of economics evaluation, which ranges from 0 (dead) to 1 (perfect health) [36]. The assumption made is that a year of life lived in perfect health is worth 1 QALY: (I year of life × 1 healthcare utility = 1 QALY). An individual's utility can change over time and due to illness. QALYs were calculated as utilities multiplied by the length of time spent in the corresponding healthcare state measured in years [37], (i.e a year lived in a bedridden state (0.5 HRQoL) × 1 year = 0.5 QALYs, is in healthcare units, similar to half a year of life lived in perfect health (1 HRQoL) x 0.5 years = 0.5 QALYs) (▶ **Table 2**).

Results

Base-case analysis

The base-case results are presented in ▶ **Table 3**, ▶ **Table 4**, and ▶ **Table 5**. A strategy was considered as dominated if comparative strategies delivered higher benefits at lower cost [38]. The UK strategy was dominated by the ACG strategy, and both of these strategies dominated the Cotton strategy (▶ **Fig. 5**). The ACG strategy (Cost £ 11,733 ($ 16,396), 12.86 QALYs) dominated the Cotton strategy (£ 10,125, 12.37 QALYs) with an incremental cost of £ 1,609 ($ 2,249), an incremental effectiveness of 0.49 and an ICER of 3,301.

Clinical events

In a 10,000-patient deterministic microsimulation, the ACG, UK and Cotton strategies generated a mean of 31, 30 and 26 endoscopic procedures per patient respectively over the modeled time horizon (▶ **Table 6**). Expectedly, the Cotton model generated the least number of endoscopic procedures due to longer surveillance intervals for non-dysplastic BE and the indefinite and LGD cohorts. The ACG model generated the largest number of dysplasia (LGD and HGD/IMC) events (▶ **Table 6**).

Sensitivity analysis

Sensitivity analyses were performed to examine the variables used in the model. Tornado diagrams comparing the ICERs for selected variables in ACG vs UK and ACG vs Cotton strategies demonstrate that the incidence of recurrent dysplasia has the greatest impact on ICERs in comparative strategies. The ICERs for each variable favors the ACG strategy in comparison with the other strategies in the overall model (▶ **Fig. 6a**, ▶ **Fig. 6b**). One-way sensitivity analysis and threshold analysis demonstrated that recurrent dysplasia had the greatest impact on the model, as demonstrated by the Tornado diagrams (▶ **Fig. 6a**, ▶ **Fig. 6b**).

Probabilistic sensitivity analysis

The ACG model was the most cost-effective strategy on PSA (▶ **Table 7**), at a mean cost of £ 11,749 ($ 16,419) (97.5 % CI 10010–14436), and effectiveness at 12.86 (12.71–13.02) QALYs. At a WTP threshold of £ 20,000, the ACG model was superior to the other strategies with the highest NMB. Acceptability curves demonstrate a crossover between the ACG and Cotton strategies at a WTP of around £ 5,000 ($ 6,987), with the acceptability curves remaining divergent for the remainder of the model, suggesting that the ACG strategy remains cost-effective over a time horizon (▶ **Fig. 7**). The UK strategy is seen to be dominated (▶ **Fig. 8**) in the model. The cost-effectiveness scatterplot highlights the overall cost-effectiveness of the ACG strategy (▶ **Fig. 8**, Supplementary material). ▶ **Fig. 9a** (Supplementary material) compares the ICERs for the ACG and Cotton strategies, with the area under the ellipse demonstrating iterations pertaining to 95 % confidence intervals (CIs). The ICERs for the ACG strategy are below the WTP threshold of £ 20,000 and indicate that this is a more cost-effective strategy. ▶ **Fig. 9b** compares the ICERs for the ACG and UK strategies, with ICERs below 0, indicating that the UK strategy is dominated.

Discussion

Surveillance post-RFA for dysplastic BE is an important and evolving topic and results from a large international multicentre study suggested that there was need for ongoing surveillance as the risk of dysplasia did not seem to plateau over time [10]. Data from this study revealed that one-quarter of post-RFA recurrences were dysplastic and nearly 41 % of these recurrences were not visible on white light endoscopic examination. Thus, there is need for ongoing surveillance to detect dysplastic recurrence. The optimal post-RFA surveillance strategy is unclear currently and there is conflicting commentary in the literature about surveillance intervals [19, 21].

In this study, we examined a cohort of patients over a 40-year time horizon, with outcomes being the development of recurrences, which were treated clinically. Age-standardized mortality data were applied to the model and the number of clinical events occurring throughout the model were captured using tracking variables. The models were designed to be as clinically realistic as possible.

We found that the ACG strategy, which involved an index endoscopy at 12 months after the primary ablative event, followed by differing surveillance intervals based on pre-RFA histology was the most cost-effective model. It also generated the greatest number of clinical events (recurrences).

The ACG strategy was more cost-effective than the UK strategy in which surveillance intervals were not determined by pre-RFA histology, even though overall numbers of endoscopies generated over the time horizon were similar in both strategies. The QALY associated with the ACG strategy was also similar to that of the UK strategy as both are endoscopy intense surveillance strategies with high rates of detection of dysplasia. However, the overall costs associated with the UK strategy is marginally greater than that of the ACG strategy and as ICERs are

▶ **Table 2** Variables and distributions used in the model.

Variable	Point estimate	Minimum value	Maximum value	Reference
Costs (£)				
▪ Cost of EGD	410	250	500	31
▪ Cost of EMR	678	400	800	31
▪ Cost of circumferential RFA	1709	700	2000	Cost of RFA catheter and procedure
▪ Cost of therapy of post RFA stricture	4663	500	5000	30,31, local costs
▪ Cost of esophagectomy	8968	7000	12000	31
▪ Annual cost PPI (regular dose)	44	44	91	30
▪ Cost of treating post RFA perforation	7166	5000	10000	30,31
Probabilities				
▪ Yearly progression of no BE to non-dysplastic BE	0.068	0.05	0.2	1–20
▪ Yearly progression of BE to LGD	0.05	0.0078	0.1	1–20
▪ Yearly progression of BE to HGD	0.01	0.0028	0.2	1–20
▪ Yearly progression of BE to EAC	0.012	0.0005	0.1	1–20
▪ Yearly progression of LGD to HGD	0.091	0.05	0.2	1–20
▪ Yearly progression of LGD to EAC	0.01	0.005	0.05	1–20
▪ Yearly progression of HGD to EAC	0.055	0.01	0.1	1–20
▪ Recurrent dysplasia 1-year post RFA	0.02	0	0.1	10
▪ Recurrent dysplasia 2 years post RFA	0.03	0	0.05	10
▪ Recurrent dysplasia 3 years post RFA	0.03	0	0.1	10
▪ Recurrent dysplasia 4 years post RFA	0.04	0	0.15	10
▪ Recurrent dysplasia 5 years post RFA	0.04	0	0.2	10
▪ Recurrent dysplasia 6 years post RFA	0.05	0	0.1	10
▪ Recurrent dysplasia 7 years post RFA	0.06	0	0.057	10
▪ Probability of Surgery for RFA perforation	0.01	0.005	0.1	27, 32
▪ RFA complication rate	0.088	0.001	0.1	27, 32
▪ Post RFA perforation	0.0001	0.00001	0.001	27, 32
▪ Post RFA stricture	0.056	4	10	27, 32
▪ Mortality post esophagectomy	0.019	0.001	0.1	27, 32
Healthcare utilities				
▪ Utility non dysplastic BE	0.91	0.8	0.99	32
▪ Utility of LGD state	0.85	0.7	0.9	32
▪ Utility of HGD state	0.77	0.4	0.8	32
▪ Utility of EAC state	0.675	0.3	0.8	32
▪ Utility post RFA state	0.77	0.7	0.9	32

EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal resection; PPI, proton pump inhibitor; BE, Barrett's esophagus; EAC, esophageal adenocarcinoma; LGD, low-grade dysplasia; HGD, high-grade dysplasia; RFA, radiofrequency ablation.

▶ **Table 2** (Continuation) Distributions used in probabilistic sensitivity analysis.

Distribution	Description	Type of distribution
▪ Distribution 1	Yearly progression of BE	Beta
▪ Distribution 2	Yearly progression of BE if pre-RFA HGD	Beta
▪ Distribution 3	Yearly progression of BE if pre-RFA LGD	Beta
▪ Distribution 4	Yearly progression of HGD	Beta
▪ Distribution 5	Yearly progression of HGD from LGD	Beta
▪ Distribution 6	Yearly progression of HGD from BE	Beta
▪ Distribution 7	Yearly progression of LGD from HGD	Beta
▪ Distribution 8	Yearly progression of LGD from LGD	Beta
▪ Distribution 9	Yearly progression of LGD from BE	Beta

EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal resection; PPI, proton pump inhibitor; BE, Barrett's esophagus; EAC, esophageal adenocarcinoma; LGD, low-grade dysplasia; HGD, high-grade dysplasia; RFA, radiofrequency ablation.

▶ **Table 3** Base-case analysis summary.

Strategy	Cost (£) Mean	Cost (£) Min	Cost (£) Max	Effectiveness (QALY) Mean	Effectiveness (QALY) Min	Effectiveness (QALY) Max
ACG	11733	227	31901	12.86	0.39	17.33
UK	11966	637	33386	12.61	0.39	17.08
Cotton	10125	227	30034	12.37	0.09	17.73

QALY, quality-adjusted life year; ACG, American College of Gastroenterology.

▶ **Table 4** Base-case analysis summary (with ICERs).

Strategy	Cost (£) Mean	Cost (£) Min	Cost (£) Max	Effectiveness (QALY) Mean	Effectiveness (QALY) Min	Effectiveness (QALY) Max
ACG	11733	227	31901	12.86	0.39	17.33
UK	11966	637	33386	12.61	0.39	17.08
Cotton	10125	227	30034	12.37	0.09	17.73

ICER, incremental cost-effectiveness ratio; ACG, American College of Gastroenterology; QALY, quality-adjusted life year.

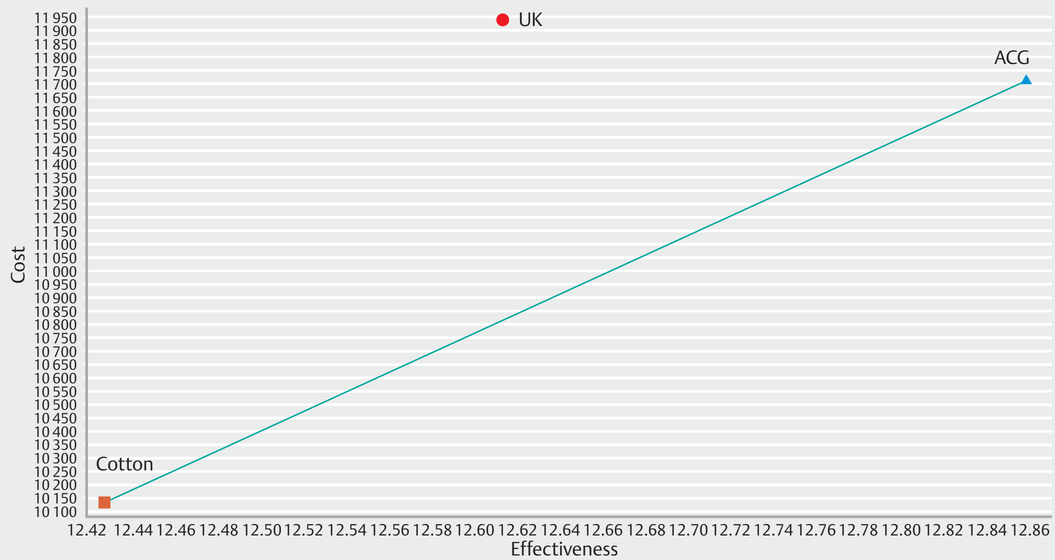
▶ **Table 5** Base-case analysis summary (excluding dominated strategies).

Strategy (excluding dominated)	Total Effect (QALYs)	Total Cost (£)	Inc. Effect	Inc. Cost	ICER	NMB at £ 20K
Cotton (undominated)	12.37	10125	–	–	–	237281
ACG (undominated)	12.86	11733	0.49	1608	3301	240196

QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; ACG, American College of Gastroenterology.

derived as (Cost A – Cost B) / (QALY A – QALY B), the overall ICER associated with the ACG strategy dominated the UK strategy from a healthcare payer perspective.

The international, multicentre study on post-RFA patients [10] found that pre-RFA dysplastic BE was associated with a significant risk of any post-RFA recurrence (non-dysplastic and dysplastic recurrence) and a significant risk of dysplastic recurrence. Conversely, the risk of dysplastic recurrence was very low if the pre-RFA histology was non-dysplastic BE. Designing surveillance intervals based on pre-RFA histology would therefore seem to be appropriate.



▶ **Fig. 5** Cost-effectiveness analysis.

▶ **Table 6** Clinical events (per 10,000 patients).

Strategy	Average no. endoscopic procedures over time-horizon per patient	No. recurrences (per 10,000 patients over a 40-year time horizon)			
		BE	LGD	HGD/IMC	Death
ACG	31	16742	8352	4735	9125
UK	30	16716	8158	4472	9100
Cotton	26	14572	7939	4519	9111

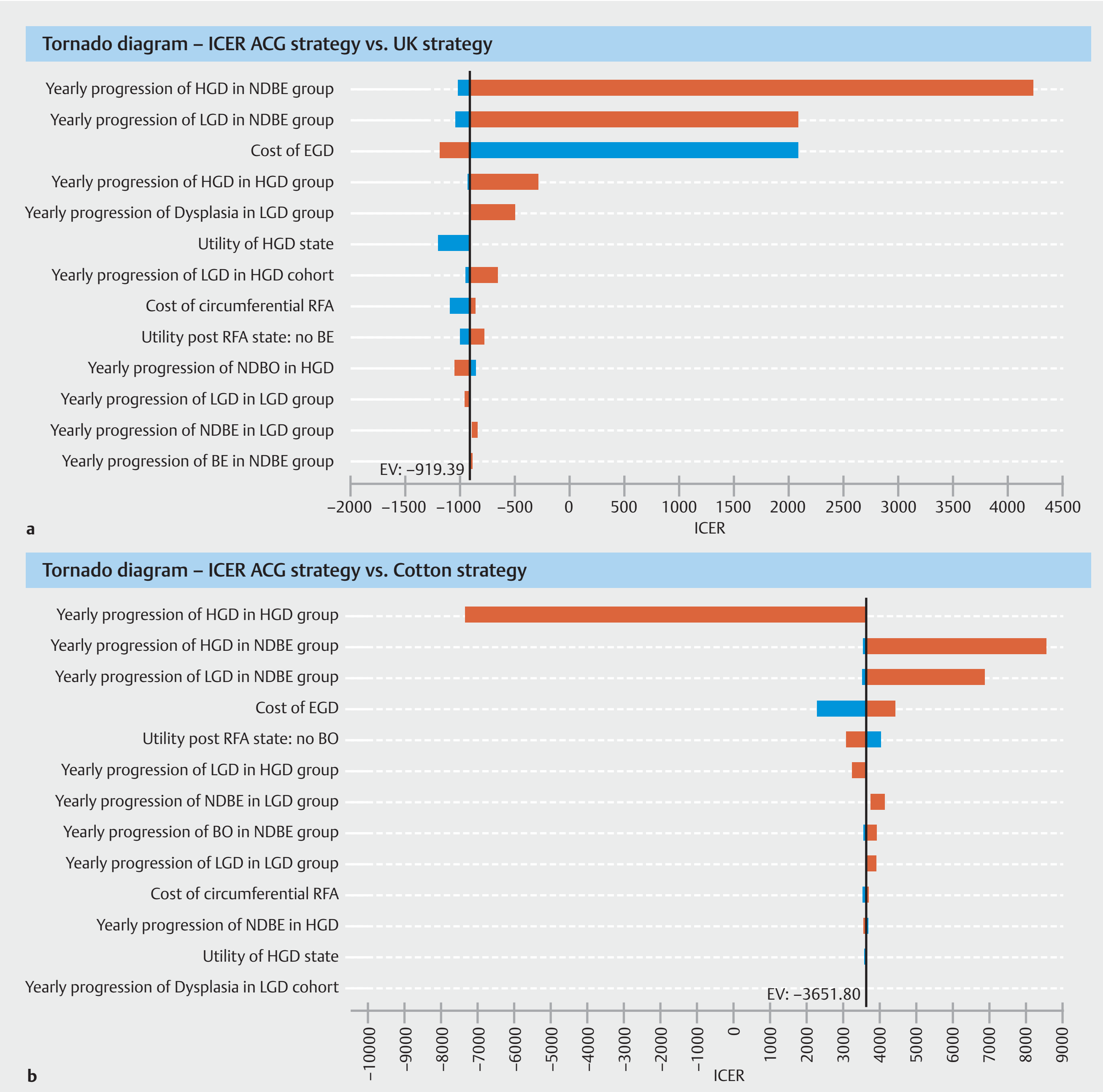
ACG, American College of Gastroenterology; BE, Barrett's esophagus; LGD, low-grade dysplasia; HGD, high-grade dysplasia; IMC, intramucosal cancer.

The Cotton model [21] had suggested surveillance based on pre-RFA histology, with surveillance intervals for pre-RFA dysplastic BE being similar to the intervals for pre-RFA dysplasia in the ACG model. The Cotton model did not suggest a clear surveillance strategy for pre-RFA non-dysplastic BE, noting that the risk of dysplasia in this cohort was very low prior to 7 years post-RFA. Despite incorporating a 3-year surveillance strategy for no BE and non-dysplastic BE, we still found that this strategy was not as cost-effective as the ACG strategy. The number of HGD recurrences detected in the Cotton strategy was lower than that of the ACG and the UK strategies, suggesting that there was an appreciable number of dysplastic recurrences in the pre-RFA non-dysplastic, low-risk cohorts over time to offset the economic benefits of infrequent surveillance endoscopies in this group in the 'expert opinion' strategy. Moreover, there is a likelihood that a less intense surveillance strategy such as the Cotton strategy (an EAC miss rate of 0.1 % was accepted in the model) could be associated with endoscopically non-resectable or advanced dysplastic/neoplastic recurrences that necessitate surgery or palliation, which would have rendered this strategy as non-cost-effective. Such an analysis was not performed given the lack of data in this regard in the literature. and would have been outside the scope of this model.

The ACG model was cost-effective in the deterministic and probabilistic analysis at the threshold used by NICE (£ 20,000 per QALY gained) in their decision-making processes [31]. Sensitivity analyses of the various variables used in the model did not alter the overall result in both deterministic and probabilistic analyses.

The differences in the model primarily relate to differential frequencies of endoscopic surveillance in the first 3 years of surveillance based on pre-RFA histology. The ACG and UK models are also similar in relation to surveillance over a time horizon. It is plausible that the cost-effectiveness curves for the three strategies diverge early and a base-case assessment at 3 years in the model confirms that the ACG strategy is the most cost-effective strategy at 3 years, but this time-frame is inadequate to incorporate the full range of sensitivity analyses and distributions in the probabilistic analysis.

Our model has various limitations that have been alluded to in our methodology. Modeling based on a payer/health system perspective does exclude some indirect and societal costs, which may be difficult to quantify and may under-estimate the overall cost-effectiveness of the interventions examined in the model. Although we have tried to provide flexibility in the model to match real-life clinical events and management strategies,

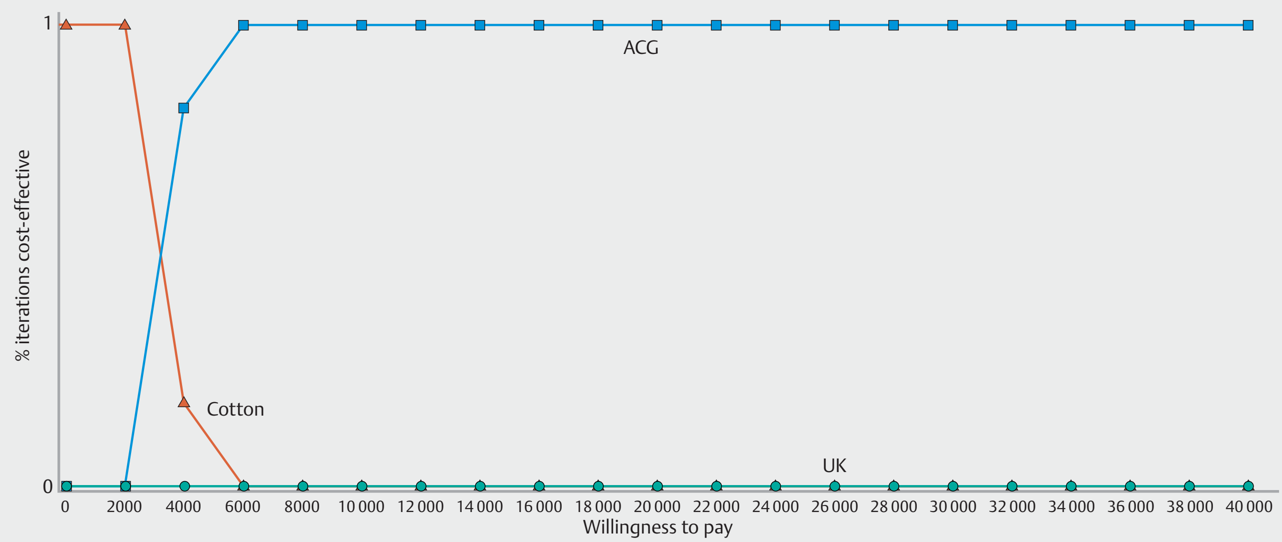


▶ **Fig. 6 a** Sensitivity analysis (ACG vs UK) Tornado diagram. **b** Sensitivity analysis (ACG vs Cotton) Tornado diagram.

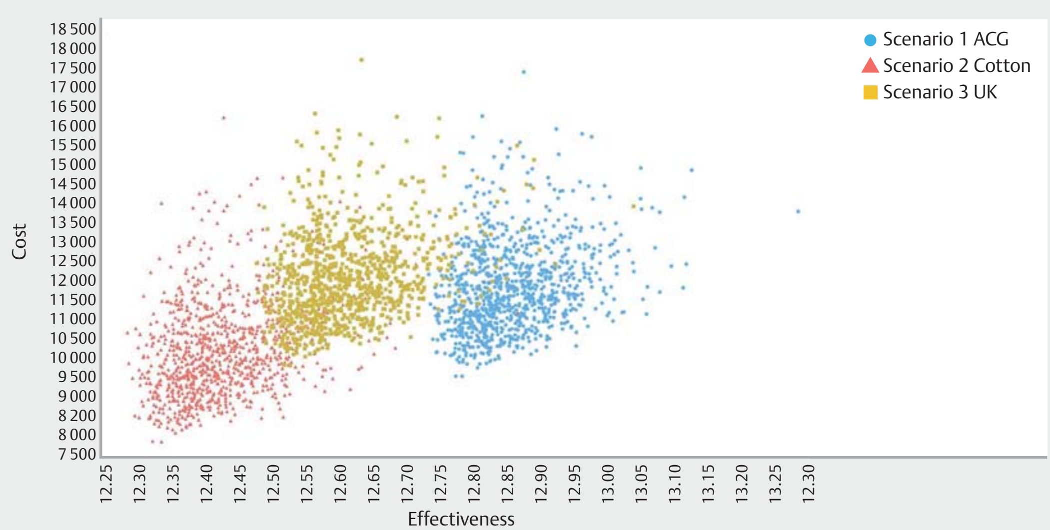
the additional inherent flaw and criticism of models are that these are unlikely to match true courses of events over a period of time. However, these are important in predicting existing and new strategies and as technology and science advances over time, strategies can change and may lead to new models with modeling being an iterative process over time.

Conclusions

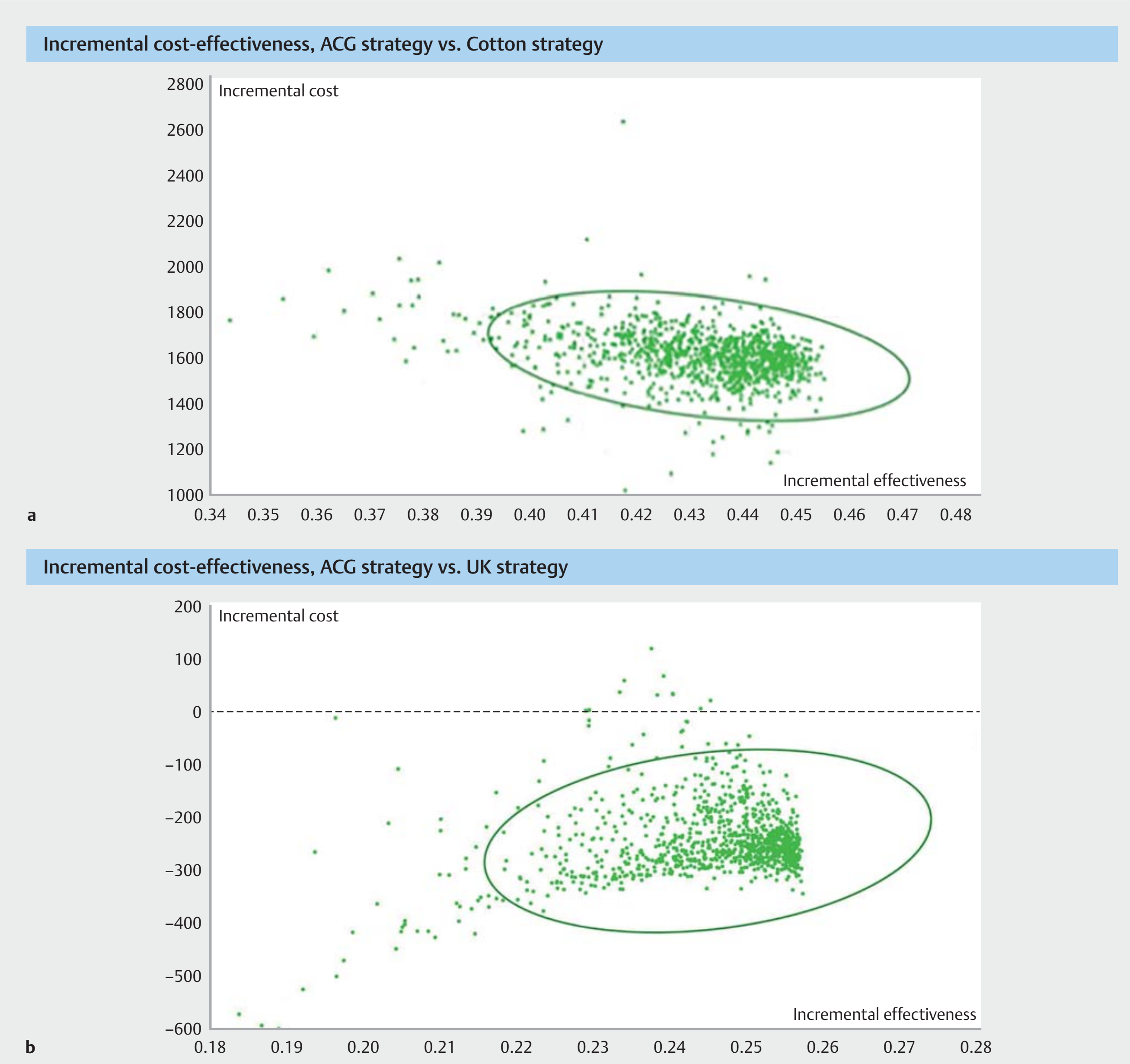
We have demonstrated in a large cohort of patients that surveillance post-RFA is important due to a distinct and significant risk of recurrent dysplasia and that designing differing surveillance intervals based on pre-RFA histology is critical.



▶ **Fig. 7** Acceptability curves (probabilistic analysis).



▶ **Fig. 8** Cost-effectiveness scatterplot.



▶ **Fig. 9** **a** ICER (ACG vs Cotton). **b** ICER (ACG vs UK).

Competing interests

The authors declare that they have no conflict of interest.

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