Taylor & Francis
Taylor & Francis Group

Expert Review of Pharmacoeconomics & Outcomes Research

ISSN: 1473-7167 (Print) 1744-8379 (Online) Journal homepage: https://www.tandfonline.com/loi/ierp20

Evaluation of the Cost-Utility of the York Faecal Calprotectin Care Pathway

Hayden Holmes, Jessica McMaster, Heather Davies, Victoria Vaines & James Turvill

To cite this article: Hayden Holmes, Jessica McMaster, Heather Davies, Victoria Vaines & James Turvill (2020): Evaluation of the Cost-Utility of the York Faecal Calprotectin Care Pathway, Expert Review of Pharmacoeconomics & Outcomes Research, DOI: 10.1080/14737167.2020.1751613

To link to this article: https://doi.org/10.1080/14737167.2020.1751613

Accepted author version posted online: 05 Apr 2020.
Published online: 19 Apr 2020.

EXPERT REVIEW OF PHARMACOECONOMICS & OUTCOMES RESEARCH
https://doi.org/10.1080/14737167.2020.1751613

Taylor & Francis
Taylor & Francis Group

ORIGINAL RESEARCH

Evaluation of the Cost-Utility of the York Faecal Calprotectin Care Pathway

Hayden Holmes [a], Jessica McMaster[a], Heather Davies[a], Victoria Vaines[b] and James Turvill[c]

[a]York Health Economics Consortium, York, UK; [b]Yorkshire and Humber Academic Health Science Network, Wakefield, UK; [c]Department of Gastroenterology, York Hospital, York Teaching Hospital NHS Foundation Trust, York, UK

ABSTRACT

Background: Lower gastrointestinal symptoms are common in the general population and it can be difficult to discriminate between inflammatory bowel disease (IBS) and irritable bowel syndrome (IBD) due to overlap of symptoms. The York Fecal Calprotectin Care Pathway (YFCCP) was introduced in 2016 as an alternative to the NICE fecal calprotectin pathway (DG11). This analysis uses the prospective data from the first 1005 patients in the YFCCP. Previous analysis demonstrated the YFCCP may be cost-saving when compared with the DG11 pathway. This analysis examined the short-term health-related quality of life (HRQoL) impact for patients in the YFCCP for IBD and IBS.

Methods: A decision tree model was used to estimate the proportion of people presenting with lower gastrointestinal symptoms that were correctly or falsely diagnosed with IBS and IBD. Time to diagnosis data was estimated and HRQoL data was estimated from published sources. Costs and QALYs were calculated for the YFCCP and each comparator.

Results: The YFCCP was cost-effective at a £20,000 threshold when compared with the current NICE recommended pathways and was cost-saving with a QALY gain (dominant)in four of the five comparators. Conclusions: The YFCCP demonstrated a QALY benefit when compared with all alternative pathways.

ARTICLE HISTORY
Received 18 December 2019
Accepted 1 April 2020

KEYWORDS
Diagnostic; Fecal calprotectin; general practice; health-related quality of life; inflammatory bowel disease; irritable bowel syndrome

1. Introduction

Discriminating between irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) is difficult due to the overlap of symptoms, such as diarrhea, stomach cramps and constipation [1,2]. Lower gastrointestinal symptoms are common amongst the general population and prompt 10% of primary care appointment and account for approximately 10% of clinical work in the NHS [3,4]. The fecal calprotectin (FC) pathway, DG11, recommended by the National Institute for Health and Care Excellence (NICE) [5], helps to discriminate between patients with IBD from those with IBS. The NICE recommendations were based on a systematic review by Waugh et al [6].

When the intestine is inflamed, calprotectin is released in excess. However, the 'normal' level of FC has not been determined and is influenced by many factors, such as age, BMI and levels of fiber intake [7]. DG11 recommends FC testing and uses a single standard cutoff value of 50 µg/g to diagnose IBD. However, the discriminatory power of this threshold is quite low. In a population with a relatively low prevalence of IBD, diagnostic accuracy is relatively poor [7]. This leads to an overestimate in IBD cases and referral for unnecessary outpatient visits and unnecessary colonoscopies.

New pathways to navigate the diagnostic uncertainty as to whether patients have IBS or IBD have been initiated over the past four years. The York Fecal Calprotectin Care Pathway [8,9] (YFCCP), implemented within the York Teaching Hospital National Health Service (NHS) Foundation Trust, was introduced in 2016 covering approximately 800,000 people. Patients aged 18 to 60 presenting to primary care practices with lower gastrointestinal symptoms are eligible for the test, provided colorectal cancer is not suspected.

In the YFCCP, rather than using a standard cutoff point of 50 µg/g, if the FC is <100 µg/g, the GP is directed to treat for IBS. There is a subsequent GP review and if the patient is still symptomatic and either over 50 years old or has a FC ≥50 µg/g, a routine referral to gastroenterology is directed. The patient will be recommended second line treatment for IBS if under 50 years old and the FC <50 µg/g, and if the patient remains symptomatic a routine referral to gastroenterology is requested. If the FC is ≥100 µg/g, a repeat test is conducted. If the repeat result is <100 µg/g, the patient is managed as stated above. If the repeat result is 100–250 µg/g, a routine referral to gastroenterology is requested, and if >250 µg/g, then an urgent referral is requested, and often a colonoscopy carried out. This is illustrated in Figure 1.

York Health Economics Consortium (YHEC) previously developed a decision tree model to determine the cost-effectiveness of the YFCCP. The results indicated that YFCCP is cost saving and of clinical benefit when compared with both published data for erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) testing [8]. However, the results indicated a trade-off when compared with published data from NICE guidance for FC testing (DG11) [5], which correctly diagnosed more patients with irritable bowel syndrome (IBS) and saved just under £18,000 in comparison [8].

The aim of the current study was to add health-related quality of life (HRQoL) data to the model in order to capture the benefit of patients spending less time in the untreated IBD or IBS health

CONTACT Hayden Holmes hayden.holmes@york.ac.uk York Health Economics Consortium, Enterprise House, Innovation Way, University of York, York YO10 5NQ, UK

Article Highlights

What is already known about this subject?

- Since the publication of the National Institute for Health and Care Excellence (NICE) guidance in 2013, there has been no agreed approach to fecal calprotectin (FC) testing in primary care.
- Using the standard 50 µg/g cut-off, many patients with irritable bowel syndrome (IBS) will have a falsely positive FC
- Previous analysis has shown the YFCCP is potentially cost-saving and uses fewer resources under certain conditions than the NICE guidance pathway for FC testing in primary care

How might it impact on clinical practice in the foreseeable future?

- The YFCCP represents an alternative approach that should be considered for diagnosis of IBD and IBS in primary care on a national level

states and more time in the treated health states. This will enable us to determine whether the YFCCP, in addition to being cost saving in most cases, also benefits HRQoL. Furthermore, the analysis will establish whether the YFCCP does result in a HRQoL loss when compared with the Waugh et al. pathway recommended in the NICE guidance (DG11) or if the differences in sensitivity and specificity are counteracted by a more efficient pathway.

2. Methods

2.1. Model overview

The decision tree model (Figures 2 and 3) was developed using Microsoft Excel and was constructed from the perspective of the United Kingdom (UK) National Health Service (NHS) and Personal Social Services (PSS). The model was adapted from a previously built model described in a paper by Turvill et al. [8], which included a hypothetical cohort of people presenting to a GP with lower gastrointestinal symptoms. The cohort then follow the York Fecal Calprotectin Care Pathway (YFCCP) or one of two comparator pathways:

- the non-FC testing pathways
- the single testing standard cutoff FC testing pathways

2.1.1. The non-FC testing pathway – comparators one and two

The first comparator pathway is one where FC testing is not used. In this pathway we have used two data sets in the model for this comparator, generating two subsets of results. The first is the published data by Tibble et al. [10] which gives the sensitivity and specificity for ESR and CRP testing to identify IBD in a low-risk patient population. The alternative set of published data is from a systematic review by Waugh et al (2013) which was used in the NICE guidance for FC testing (DG11). These are comparators one and two in the results respectively.

2.1.2. The standard cutoff FC testing pathway – comparators three, four and five

This pathway assumes the GP has assessed the patient using the suggested FC cutoff of <50 µg/g used in the current NICE guidance DG11. Three data sets were used in the model, generating three subsets of results. The first was observed patient data from the YFCCP whereby the sensitivity and specificity was calculated based on what would have happened, had this cohort been referred according to the NICE pathway instead of using the intervention pathway. The second and third data sets were the Tibble et al data from the Department of Health, NHS Purchasing and Supply Agency, Center for Evidence-based Purchasing (CEP) review (2002) [10] and the Waugh et al data used in the NICE Guidelines (2013) [6] where the cohort would be referred according to the NICE pathway. These are comparators three, four and five in the results respectively.

A one-year time horizon was used so discounting was not necessary [11]. The effectiveness of the pathways was determined by the sensitivity and the specificity of each test. Patient level benefits were quantified in the model using quality adjusted life years (QALYs) and the main outcome measure was an incremental cost effectiveness ratio (ICER). Other outcome measures included the net monetary benefit, the number of correctly diagnosed IBS or IBD cases, the number of unnecessary colonoscopies (caused by false positive tests) and the number of secondary clinician appointments.

2.2. Model inputs

A summary of the effectiveness and resource use inputs can be found in the paper published by Turvill et al [8]. The unit costs were updated to 2019 (Table 1) and where possible, were identified from publically available sources. The effectiveness results have been updated with the most recent observational data (Table 2). The NHS 2017–18 National Schedule of Reference Costs was used for hospital-based resource use. This included the cost of a specialist visit and a colonoscopy. The Personal Social Services Research Unit (PSSRU) [12] costs were applied to resource use in primary care (e.g. GP visits). Furthermore, the British National Formulary (BNF) [13] was used for pharmaceutical costs.

2.2.1. Addition of HRQoL to the existing cost-effectiveness model

HRQoL was added to the existing cost-effectiveness model by using published utility values for treated and untreated IBS and IBD (Table 3). In order to apply these to the decision tree pathways, the number of days untreated in a year was calculated for a true positive, true negative, false positive and false negative diagnosis (the four outcomes in the decision tree) for the intervention and each comparator as shown in Figures 2 and 3. The proportion of the year a person is treated and untreated was calculated, and this was multiplied by the relevant utility value for treated and untreated IBS or IBD to calculate the number of QALYs in the pathway per person.

The time in the pathway was calculated in the model using estimates of wait time for tests, GP appointments and GP follow ups, outpatient appointments and colonoscopies. These estimates were informed by published sources, YFCCP trial data, and clinical advice from York Hospital. The summary of time to diagnosis is displayed in Table 4.

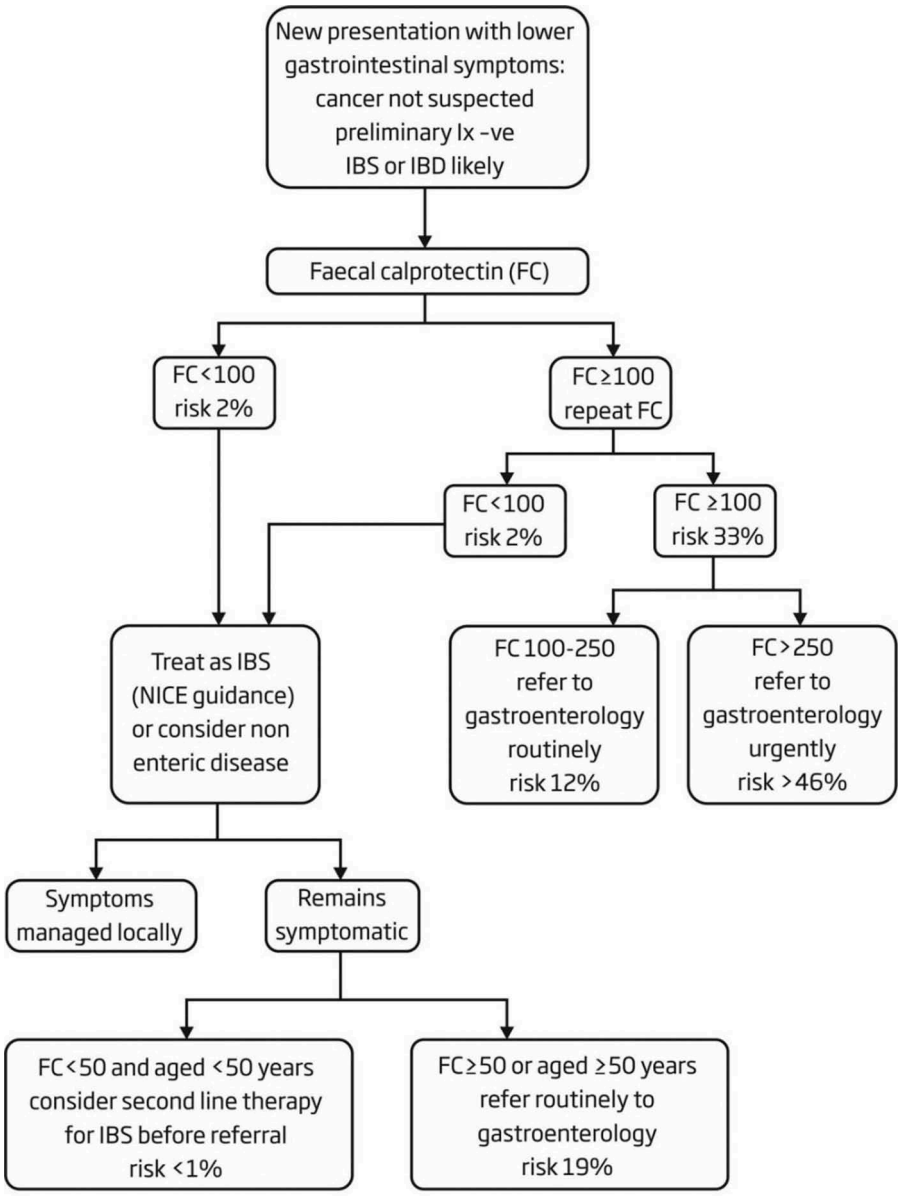

Figure 1. York fecal calprotectin care diagnostic pathway.

2.3. Deterministic sensitivity analysis

Deterministic sensitivity analysis was conducted to account for any uncertainly around the parameters and to observe the key drivers affecting the cost-effectiveness results. Tornado diagrams were created. The parameters included were:

- IBD prevalence
- days in a year people were in a pathway untreated and treated
- the sensitivity and specificity of the pathways
- the utility values used in the model
- the costs

Where possible, published values were used when varying the parameters, otherwise the parameters were varied by 10%.

3. Results

3.1. Base case

The results of the cost-effectiveness model are presented in Table 5. Using a £20,000 threshold value commonly used in UK NHS reimbursement decision making, the YFCCP pathway may be cost-effective when compared with the alternative, no FC and FC pathways. YFCCP is dominant (cost-saving with a QALY gain) when compared with four of the five pathways. It was only when compared with the NICE published efficacy of standard FC testing (Waugh et al) that the YFCCP resulted in additional costs. The incremental cost was over £14,000 but this resulted in an additional 1.62 incremental QALYs per 1000 patients, giving an ICER of just under £8,850/QALY. The addition of HRQoL to the existing cost-effectiveness model published by Turvill et al. [8] demonstrated a QALY benefit when compared with all alternative pathways.

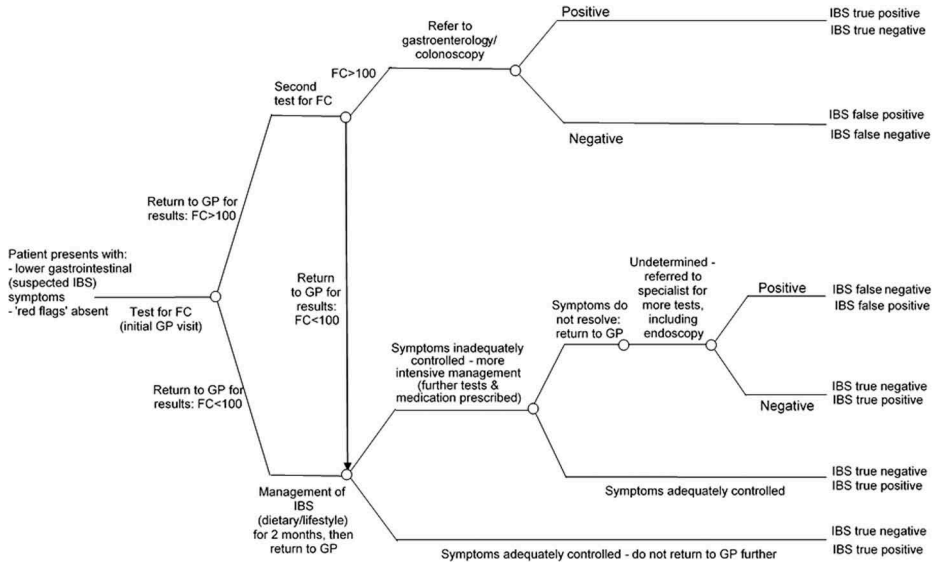

Figure 2. Decision tree model: York fecal calprotectin care pathway.

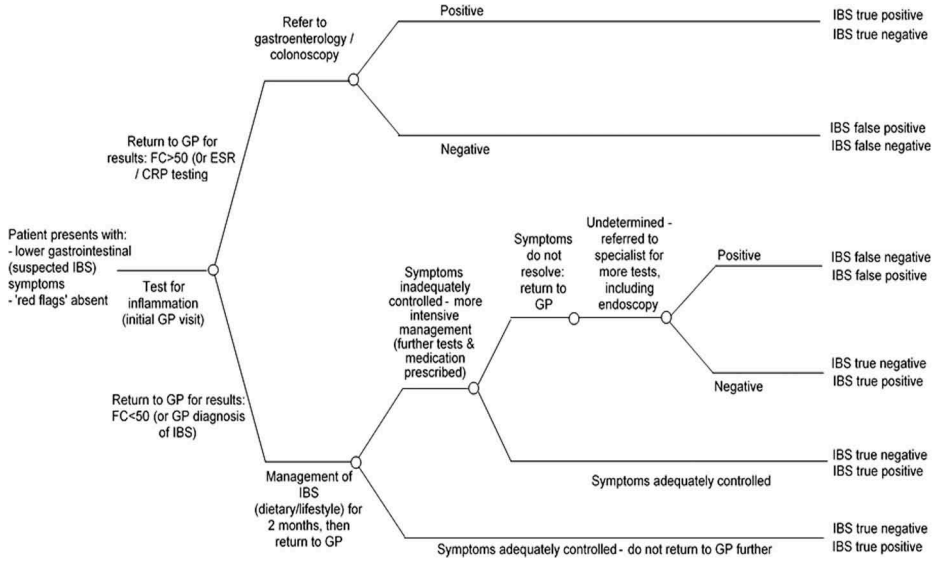

Figure 3. Decision tree model: standard point cutoff and single test as assumed in current NICE guidance (FC <50mcg/g) or no FC available using ESR/CRP.

3.2. Deterministic analysis

Figure 4 presents the tornado diagrams for each comparator, resulting from varying individual inputs in the economic model. Varying the inputs by 10% in three of the five comparators (Tibble et al. no FC testing, YFCCP data using the standard cut off and Tibble et al published FC testing) did not affect the main results, with the net monetary benefit staying above zero in all cases.

When comparing YFCCP with the GP pathway, the net monetary benefit falls below zero when the specificity of the GP pathway increases to 88%, and when the days untreated (with a true negative diagnosis) increases above 53 days in the intervention (YFCCP).

Inputs are most sensitive to change when comparing YFCCP with the Waugh published FC testing data. Varying the specificity and the days untreated in all diagnosed patients can lead to the intervention no longer being cost-effective.

4. Discussion

The aim of this study was to determine whether the YFCCP, in addition to being cost saving in four out of five cases (as shown by an existing economic model), also benefits HRQoL. This was carried out by adding HRQoL data to the existing model [8] to capture the benefit of patients spending less time in untreated IBD or IBS health states and more time in treated health states. The model estimates that the YFCCP is likely to be cost-effective in the UK at a £20,000 threshold, when compared with the alternative pathways described previously. The addition of HRQoL to the existing cost-effectiveness model demonstrated a QALY benefit when compared with all alternative pathways.

There is a material difference between the HRQoL of an untreated or treated IBS or IBD patient (incremental difference of 0.13 and 0.4 respectively). IBD can affect a person not only physically, but also mentally, by causing issues with sleep, anxiety and depression [14–17]. The QALY benefit when

Table 1. Updated unit costs used in the model*.

Description of event	Unit cost (£)	Source
GP visit	37.40	Personal Social Services Research Unit [11]
FC test	23.82	NICE Medtech innovation briefing (MIB132) [13]
ESR + CRP test	5.85	NICE Medtech innovation briefing (MIB132) [13]
IBS medication (first line)**	22.34	NHS Electronic Drug Tariff, March 2019 [14]
IBS medication (second line)***	76.82	NHS Electronic Drug Tariff, March 2019 [14]
Outpatient gastroenterology appointment (consultant led)	155.61	NHS reference costs 2017–18 SC301 [15]
Colonoscopy	263.67	NHS reference costs 2017–18 FE32Z [15]

*All costs inflated to 2019 values using PSSRU inflation index
**(loperamide, mebeverine, ipaghula husk)[1]
***(Amitriptyline hydrochloride, linaclotide)[2]; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; FC: fecal calprotectin; GP: general practitioner; IBS: irritable bowel syndrome; NHS: national health service; NICE: national institute for health care excellence

Table 2. Diagnostic accuracy for each of the pathways.

Test	Sensitivity	Specificity	Source
Intervention (YFCCP data)	94%	92%	Turvill et al [8]
No FC testing (ESR + CRP) (Tibble et al)	35%	73%	Tibble et al [9]
GP Pathway (NICE)	100%	79%	NICE DG11 [5]
Standard cut off (YFCCP data)	96%	60%	Calculated from YFCCP data
Published FC testing (Tibble et al)	90%	80%	Tibble et al [9]
Published FC testing (NICE)	93%	94%	NICE DG11 [5]

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; FC: fecal calprotectin; GP: general practitioner; IBS: irritable bowel syndrome; NICE: national institute for health care excellence; YFCCP: York fecal calprotectin care pathway

Table 3. HRQoL model inputs.

Health state	Utility value	Source
Untreated IBS	0.68	NICE CG61 (2008) [16]
Treated IBS	0.81	NICE CG61 (2008) [16]
Untreated IBD	0.43	Weighted average of Crohn's disease (39%, NICE NG129 [17]) and Ulcerative Colitis (61%, NICE TA163 [18]). Proportions based on Turvill et al. [8]
Treated IBD	0.83	

HRQoL: health-related quality of life; IBD: inflammatory bowel disease; IBS: irritable bowel syndrome; NICE: national institute for health care excellence

Table 4. Time to correct diagnosis for each pathway.

	Time to correct diagnosis (days)		
	YFCCP	No FC testing	Standard cutoff
True positive	66	82	83
False positive	66	82	83
True negative	44.35	39.35	44.35
False negative	148	143	148

FC: fecal calprotectin; YFCCP: York fecal calprotectin care pathway

a cohort follows the YFCCP pathway in comparison to the Waugh et al. FC pathway, may outweigh the extra cost associated with it, because the cohort enjoys a net increase in HRQoL over the course of the diagnosis pathway. However, despite being cost-effective at the £20,000 threshold, a trade-off still stands between the YFCCP and Waugh et al pathways, with this comparator pathway diagnosing more IBS cases correctly (864 correct diagnosis compared with 845, or 2% more cases identified), and minimal difference (less than 0.5% difference) between the correctly diagnosed IBD cases.

There are limitations to the current study. Due to the lack of evidence-based literature surrounding the number of days spent in the treated and untreated health state in the time horizon of one year, it was necessary to make assumptions based on input from clinical experts. Further to this, the time to treatment could vary widely between locations due to differing waiting times for different GPs and hospitals. Because the HRQoL values were derived from time to treatment, in practice, the QALY benefits would differ depending on the wait times for each GP practice.

One of the benefits of the YFCCP when compared with Waugh et al was the faster time to diagnosis for the true positive patients in the YFCCP. This was possible because the YFCCP includes urgent referrals for a subpopulation with a second FC test of >250 µg/g. It would be pertinent to see if this urgent referral process would maintain the faster diagnosis time outside of a trial environment.

Deterministic sensitivity analysis (DSA) was conducted on all of the model inputs to identify which inputs the model results were most sensitive to. DSA highlights that variation in the model inputs is unlikely to affect the results to the extent that the YFCCP would not be cost-effective at the £20,000 threshold in most cases (Figure 4). The key uncertainties occur only when the YFCCP is compared to the Waugh et al pathway. The biggest drivers of the model results were:

- number of days untreated in the true negative pathway – Waugh et al
- number of days untreated in the true negative pathway – YFCCP
- days in pathway untreated in the true positive pathway – Waugh et al
- days in pathway untreated in the true positive pathway – YFCCP
- the specificity of Waugh et al

4.1. Number of days untreated in the true negative pathway

If the untreated days in the YFCCP rise above 47.25 days in a year and the number of untreated days in the Waugh et al

Table 5. Summary of results.

Comparators one and two – No FC testing	YFCCP	No FC	Incremental
Tibble et al [9]			
Total costs	£211,807	£258,671	-£46,864
Total QALYs	789.61	783.56	6.05
ICER			Dominant
NMB			£167,806
Waugh et al – GP pathway [6]			
Total costs	£211,807	£232,407	-£20,600
Total QALYs	789.61	787.92	1.69
ICER			Dominant
NMB			£54,474
Comparators three four and five – FC testing with ≥50 µg/g cutoff	YFCCP	Single FC ≥50 µg/g	Incremental
YFCCP as single test FC cutoff ≥50 µg/g			
Total costs	£211,807	£313,944	-£102,137
Total QALYs	788.71	783.66	5.04
ICER			Dominant
NMB			£203,030
Tibble et al [9]			
Total costs	£211,807	£245,377	-£33,570
Total QALYs	789.61	785.97	3.64
ICER			Dominant
NMB			£106,274
Waugh et al [6]			
Total costs	£211,807	£197,435	£14,372
Total QALYs	789.61	787.99	1.62
ICER			£8,847
NMB			£18,119

FC: fecal calprotectin; ICER: incremental cost-effectiveness ratio; NMB: net monetary benefit; QALY: quality adjusted life years; YFCCP: York Fecal Calprotectin Care Pathway

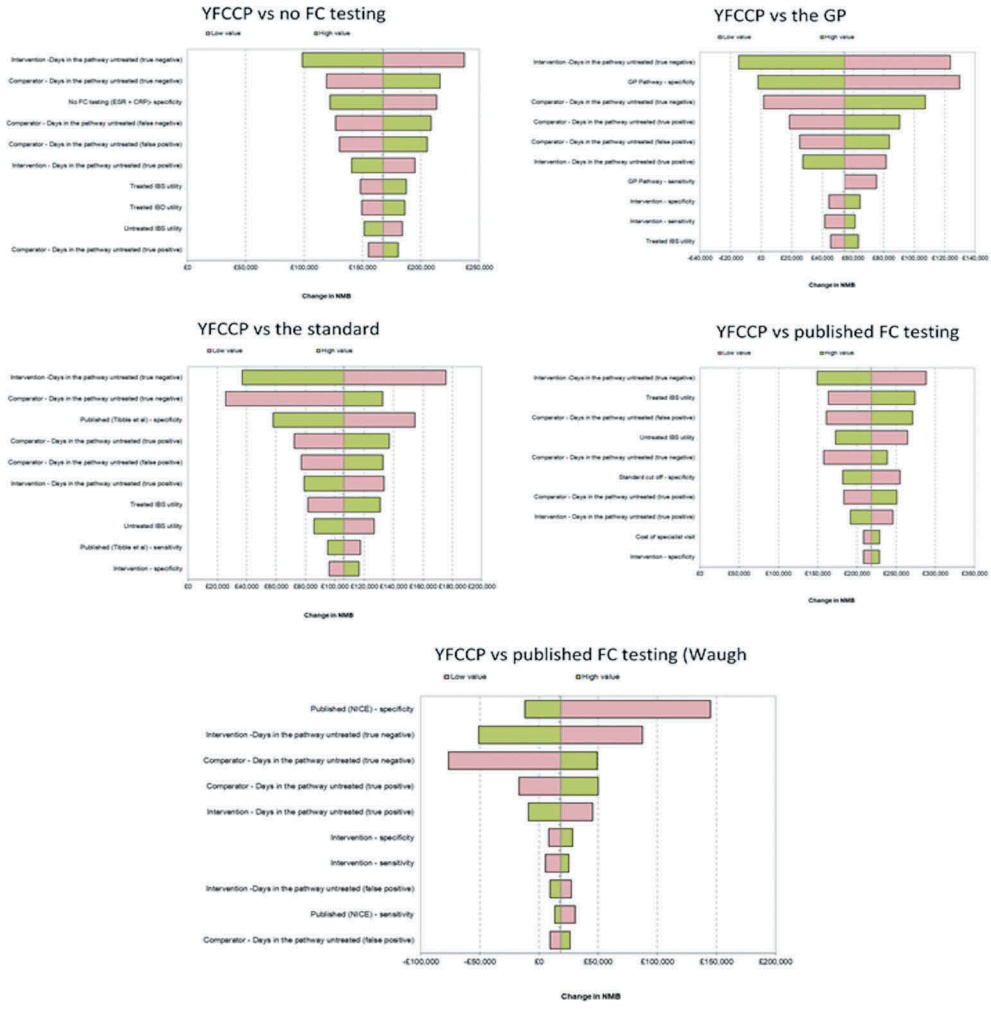

Figure 4. Tornado diagrams.

pathway are held constant at 44.35 days, the YFCCP is no longer cost effective at the £20,000 threshold when compared with the Waugh et al FC pathway. This is partly due to a higher number of treated days with an improved HRQoL in the Waugh et al. FC pathway. The number of untreated days in the YFCCP for those with a true negative diagnosis has the biggest effect on the incremental change in QALYs. Once the number of untreated days rise above 49, the incremental QALY benefit falls below zero compared with the Waugh et al FC pathway. However, it is unlikely that the number of untreated days would differ between these two pathways.

4.2. Number of days untreated in the true positive pathway

Even though the YFCCP includes an extra FC test, the time to diagnosis for true positives is quicker in the YFCCP. This is because the YFCCP better identifies the most at-risk patients and they can be sent with urgent referral for a diagnostic colonoscopy and subsequent treatment. This results in a more efficient pathway with previous analysis [8]. The estimated overall time spent in the diagnostic pathway for true positives was 66 and 83 days for the YFCCP and Waugh et al pathways respectively. The YFCCP stops being cost effective at the £20,000 threshold once the total time in the true positive pathway is above 77 days. If the total time to diagnosis was assumed to be 83 days for both the YFCCP and Waugh et al pathways the ICER would be approximately £63,000 per QALY.

The efficiency of a chosen IBS/IBD diagnostic pathway carries particular significance because of the clinical context in which it occurs. Firstly, whilst few patients will die from IBD, delayed diagnosis increases the risk of complications and the need for surgery and so early diagnosis has become a NICE quality standard (QS81) [18–20]. Secondly more accurate diagnosis means the reduction in colonoscopies frees up colonoscopy resource which may then be directed toward patients with suspected colorectal cancer.

4.3. Specificity of the Waugh et al pathway

The lower the diagnostic specificity with the Waugh pathway, the higher the benefit of the YFCCP. It is only when the specificity of the Waugh et al pathway is above 97% that the Waugh pathway becomes more cost-effective than the YFCCP at a £20,000 threshold. However, even when the Waugh pathway specificity rises to 100%, the YFCCP still brings a positive QALY benefit.

In conclusion, the YFCCP has been shown to be cost-saving against four out of five pathways and it is cost-effective against the Waugh pathway at an ICER of £20,000. The YFCCP demonstrates a QALY benefit against all comparators. It would be beneficial to have real-world data for the number of days treated for individual GP practices or Clinical Commissioning Group (CCG) areas, so each practice can assess whether introducing the YFCCP is beneficial for them.

Notes

1. As recommended in NICE clinical guideline for IBS, CG 61, https://www.nice.org.uk/guidance/cg61/chapter/1-Recommendations#pharmacological-therapy.
2. As recommended in NICE clinical guideline for IBS, CG 61, https://www.nice.org.uk/guidance/cg61/chapter/1-Recommendations#pharmacological-therapy.

Declaration of interest

JM (at the time of analysis), HD and HH work for York Health Economics Consortium, a consultancy company, who was commissioned by the Yorkshire & Humber AHSN to undertake the original analysis. There is no further support from any organization for the submitted work and no further financial relationships with any organizations that might have an interest in the submitted work in the previous three years.

Author contribution

HH developed the original YHEC model and conducted the original analysis. JT and VV contributed to the YHEC analysis. HH and JM built the adapted model. JT contributed to the adapted model. HD, HH and JT drafted the manuscript.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Funding

The YHEC analysis was supported by the Yorkshire & Humber AHSN.

ORCID

Hayden Holmes http://orcid.org/0000-0003-2559-061X

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Abdul Rani R, Raja Ali RA, Lee YY. Irritable bowel syndrome and inflammatory bowel disease overlap syndrome: pieces of the puzzle are falling into place. Intest Res. 2016;14(4):297–304.
2. Weimers P, Burisch J. The Importance of Detecting Irritable Bowel-like Symptoms in Inflammatory Bowel Disease Patients. J Crohns Colitis. 2018;12(4):385–386.
3. Drossman DA, Camilleri M, Mayer EA, et al. AGA technical review on irritable bowel syndrome. Gastroenterology. 2002;123(6):2108–2131.
4. Jones R, Hunt C, Stevens R, et al. Management of common gastrointestinal disorders: quality criteria based on patients' views and practice guidelines. Br J Gen Pract. 2009;59(563):415–421.
5. National Institute for Health and Care Excellence (NICE). Faecal calprotectin diagnostic tests for inflammatory diseases of the bowel. DG11.: NICE. 2013. Available from: https://www.nice.org.uk/guidance/dg11/resources/faecal-calprotectin-diagnostic-tests-for-inflammatory-diseases-of-the-bowel-pdf-1053624751045
6. Waugh N, Cummins E, Royle P, et al. Faecal calprotectin testing for differentiating amongst inflammatory and non inflammatory bowel diseases: systematic review and economic evaluation. Health Technol Assess. 2013;17:55.
7. Mendall MA, Chan D, Patel R, et al. Faecal calprotectin: factors affecting levels and its potential role as a surrogate marker for risk of development of Crohn's Disease. BMC Gastroenterol. 2016;16(1):126.

8. Turvill J, Turnock D, Holmes H, et al. Evaluation of the clinical and cost-effectiveness of the York Faecal Calprotectin Care Pathway. Frontline Gastroenterol. 2018;9(4):285.
9. Turvill J. The York Faecal Calprotectin Care Pathway for use in primary care. 2018. Available from: http://www.ahsn-nenc.org.uk/wp-content/uploads/2018/06/James-Turvill.pdf
10. Tibble JA, Sigthorsson G, Foster R, et al. Use of surrogate markers of inflammation and Rome criteria to distinguish organic from non-organic intestinal disease. Gastroenterology. 2002;123(2):450–460.
11. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013. NICE; 2013. Available from: https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781
12. Personal Social Services Research Unit (PSSRU). Unit Costs of Health and Social Care 2018. Kent Uo. 2018.
13. National Institute for Health and Care Excellence (NICE). BNF. NICE. 2019. Available from: https://bnf.nice.org.uk/
14. Goodhand JR, Wahed M, Mawdsley JE, et al. Mood disorders in inflammatory bowel disease: relation to diagnosis, disease activity, perceived stress, and other factors. Inflamm Bowel Dis. 2012;18(12):2301–2309.
15. Ananthakrishnan AN, Khalili H, Pan A, et al. Association between depressive symptoms and incidence of Crohn's disease and ulcerative colitis: results from the Nurses' Health Study. Clin Gastroenterol Hepatol. 2013;11(1):57–62.
16. Loftus EV Jr., Guerin A, Yu AP, et al. Increased risks of developing anxiety and depression in young patients with Crohn's disease. Am J Gastroenterol. 2011;106(9):1670–1677.
17. Ranjbaran Z, Keefer L, Farhadi A, et al. Impact of sleep disturbances in inflammatory bowel disease. J Gastroenterol Hepatol. 2007;22(11):1748–1753.
18. Nahon S, Lahmek P, Paupard T, et al. Diagnostic Delay Is Associated with a Greater Risk of Early Surgery in a French Cohort of Crohn's Disease Patients. Dig Dis Sci. 2016;61(11):3278–3284.
19. Nguyen VQ, Jiang DF, Hoffman SN, et al. Impact of Diagnostic Delay and Associated Factors on Clinical Outcomes in a US Inflammatory Bowel Disease Cohort. Inflamm Bowel Dis. 2017;23(10):1825–1831.
20. Schoepfer AM, Dehlavi MA, Fournier N, et al. Diagnostic Delay in Crohn's Disease Is Associated With a Complicated Disease Course and Increased Operation Rate. Am J Gastroenterol. 2013;108(11):1744–1753.