Appendix

1-1. Structured searches of PubMed

Table S1 Structured searches in PubMed to identify epidemiology data relevant to modelling

Index	Aim	Search string	Hits
1	All incidence studies	"Incidence"[Majr] or "Incidence"[ti] OR "Epidemiology/economics"[Majr] OR "Epidemiology/prevention and control"[Majr] OR "Epidemiology/statistics and numerical data"[Majr] OR "Epidemiology/trends"[Majr] OR "Epidemiology/utilization"[Majr] OR "prevalence"[Majr] or "Prevalence"[ti]	185,755
2	All studies since 2010	"2010/01/01"[PDAT]: "2016/11/01"[PDAT]	6,835,390
3	Recent incidence studies	#1 AND #2	66,350
4	Those reporting on inflammatory bowel diseases	"Crohn Disease"[Mesh] or "Colitis, Ulcerative"[Mesh] or "Inflammatory Bowel Diseases"[Mesh] or "Crohn Disease"[tiab] or "Crohn's Disease"[tiab] or "Ulcerative Colitis"[tiab] or "Inflammatory Bowel Disease"[tiab]	87,690
5	incidence of inflammatory bowel diseases	#3 AND #4	495
6	Containing abstracts	hasabstract[text]	16,754,729
7	Language	english[lang] OR german[lang] OR french[lang]	23,563,841
8	Avoid non-primary research	"Case Reports" [Publication Type] OR "Clinical Conference" [Publication Type] OR "Comment" [Publication Type] OR "Editorial" [Publication Type] OR "Guideline" [Publication Type] OR "Review" [Publication Type]	4,806,491
9	Animal studies	See Hoojimans et al.[1]	6,228,155
10	Final reference list	#5 AND # 6 AND # 7 NOT # 8 NOT # 9	408

Table S2 Structured searches in PubMed to identify cost data relevant to modelling

Index	Aim	Search string	Hits
1	All cost studies	"Costs and Cost Analysis"[Mesh] OR "Cost-Benefit Analysis"[Mesh] OR "Cost of Illness"[Mesh] OR "Health Care Costs"[Mesh] OR "Cost Sharing"[Mesh] OR "Cost Savings"[Mesh] OR "Technology, High-Cost"[Mesh] OR "Cost Control"[Mesh] OR "Cost Allocation"[Mesh] OR "Direct Service Costs"[Mesh] OR "Hospital Costs"[Mesh] OR "Employer Health Costs"[Mesh] OR "Drug Costs"[Mesh] OR "Health Expenditures"[Mesh] OR "Health Resources/economics"[Mesh] OR "Economics, Hospital"[Mesh] OR "Economics, Medical"[Mesh] OR "Economics, Pharmaceutical"[Mesh] OR "Economics, Nursing"[Mesh] OR "Managed Care Programs"[Mesh] OR "Insurance, Physician Services"[Mesh] OR "Budgets"[Mesh] OR "Economics"[Mesh] OR "Commerce"[Mesh] OR Cost[tiab] OR economic[tiab] OR ((EURO[tiab] OR EUROS[tiab] OR GBP[tiab] OR USD[tiab] OR dollar*[tiab] OR pounds[tiab]) AND (Cost[tiab] OR price[tiab] or expense[tiab] OR burden[tiab]))	876,295
2	All studies since 2010	"2010/01/01"[PDAT]: "2016/11/01"[PDAT]	6,835,390
3	Recent cost studies	#1 AND #2	278,260
4	Those reporting on inflammatory bowel diseases	"Crohn Disease"[Mesh] or "Colitis, Ulcerative"[Mesh] or "Inflammatory Bowel Diseases"[Mesh] or "Crohn Disease"[tiab] or "Crohn's Disease"[tiab] or "Ulcerative Colitis"[tiab] or "Inflammatory Bowel Disease"[tiab]	87,690
5	Cost of inflammatory bowel diseases	#3 AND #4	835
6	Containing abstracts	hasabstract[text]	16,754,729
7	Language	english[lang] OR german[lang] OR french[lang]	23,563,841
8	Avoid non-primary research	"Case Reports" [Publication Type] OR "Clinical Conference" [Publication Type] OR "Comment" [Publication Type] OR "Editorial" [Publication Type] OR "Guideline" [Publication Type] OR "Review" [Publication Type]	4,806,491
9	Animal studies	See Hoojimans et al.[1]	6,228,155
10	Final reference list	#5 AND # 6 AND # 7 NOT # 8 NOT # 9	482

Table S3 Structured searches in PubMed to identify health state utility and disutility relevant to modelling

Index	Aim	Search string	Hits
1	All quality of life studies	(("Quality of Life"[Mesh] OR EuroQol[tiab] OR EQ5D[tiab] OR SF36[tiab] OR ((“short-form”[tiab] OR “short form”[tiab]) AND (survey[tiab] OR questionnaire[tiab])) OR ((“health-related”[tiab] OR “health related”[tiab] OR “health state”[tiab] OR “health-state”[tiab]) AND (utility[tiab] OR utilities[tiab] OR disutility[tiab] OR disutilities[tiab] OR "quality of life"[tiab] OR QOL[tiab])) OR “patient preference”[tiab] OR “patient satisfaction”[tiab]))	185,828
2	All studies since 2010	"2010/01/01"[PDAT]: "2016/11/01"[PDAT]	6,835,390
3	Recent quality of life studies	#1 AND #2	85,619
4	Those reporting on inflammatory bowel diseases	"Crohn Disease"[Mesh] or "Colitis, Ulcerative"[Mesh] or "Inflammatory Bowel Diseases"[Mesh] or "Crohn Disease"[tiab] or "Crohn's Disease"[tiab] or "Ulcerative Colitis"[tiab] or "Inflammatory Bowel Disease"[tiab]	87,690
5	Cost of inflammatory bowel diseases	#3 AND #4	831
6	Containing abstracts	hasabstract[text]	16,754,729
7	Language	english[lang] OR german[lang] OR french[lang]	23,563,841
8	Avoid non-primary research	"Case Reports" [Publication Type] OR "Clinical Conference" [Publication Type] OR "Comment" [Publication Type] OR "Editorial" [Publication Type] OR "Guideline" [Publication Type] OR "Review" [Publication Type]	4,806,491
9	Animal studies	See Hoojimans et al.[1]	6,228,155
10	Final reference list	#5 AND # 6 AND # 7 NOT # 8 NOT # 9	616

Table S4 Structured searches in PubMed to identify efficacy data from randomized, controlled, clinical trials and meta-analyses

Index	Aim	Search string	Hits
1	All pill-capsule endoscopy or PillCam studies	"Capsule Endoscopes"[Mesh] or PillCam[tiab] or “capsule endoscopy”[tiab] or “colon capsule”[tiab] or “capsule colonoscopy”[tiab] or “capsule enteroscopy”[tiab] or “small bowel colon capsule”[tiab]	3,264
2	All studies since 2000	"2000/01/01"[PDAT]: "2016/11/01"[PDAT]	13,263,192
3	Recent intervention studies	#1 AND #2	3,258
4	Those reporting on Randomized controlled trials (RCT)	((("Clinical Trial"[tiab] or "Clinical study"[tiab] or "Clinical studies"[tiab] or "Clinical Trials"[tiab] OR "prospective study"[tiab] OR "prospective trial"[tiab]) AND ((randomized[tiab] OR randomised[tiab]) AND (blinded[tiab] OR controlled[tiab]))) OR "Randomized Controlled Trials as Topic"[Mesh] OR "Clinical Trial"[Publication Type] OR RCT[tiab] OR "Comparative Study"[Publication Type] OR "Meta-Analysis"[Publication Type] OR meta-analysis[tiab] OR (indirect[tiab] AND “treatment comparison”[tiab]))	2,482,001
5	RCT and PillCam studies of interest	#3 AND #4	537
6	Containing abstracts	hasabstract[text]	16,781,271
7	Language	english[lang] OR german[lang] OR french[lang]	23,594,623
8	Avoid non-primary research	"Case Reports" [Publication Type] OR "Clinical Conference" [Publication Type] OR "Comment" [Publication Type] OR "Editorial" [Publication Type] OR "Guideline" [Publication Type] OR "Review" [Publication Type]	4,811,358
9	Animal studies	See Hoojimans et al.[1]	6,233,072
10	Capsule endoscopy efficacy studies in humans	#5 AND # 6 AND # 7 NOT # 8 NOT # 9	435
11	Those reporting on inflammatory bowel diseases	"Crohn Disease"[Mesh] or "Colitis, Ulcerative"[Mesh] or "Inflammatory Bowel Diseases"[Mesh] or "Crohn Disease"[tiab] or "Crohn's Disease"[tiab] or "Ulcerative Colitis"[tiab] or "Inflammatory Bowel Disease"[tiab]	87,812
12	Final reference list	#10 AND #11	93

1-2. Patient population summary characteristics

Table S5 Model population

Characteristic	Mean	Source
Age	42	[2]
Age at diagnosis	30	Illinois Gastroenterology Group Project Sonar Database
Gender, % male	43.5	[3]
Weight	83.6[a]	[4]
CDAI score	220	Assumption
Ileal (L1), %	25.69	[5]
Colonic (L2), %	18.48	[5]
Ileocolonic (L3), %	39.97	[5]
Upper GI (L4), %	15.86	[5]
Superficial ulcers, %	30	Illinois Gastroenterology Group Project Sonar Database
Deep ulcers, %	12.2	Illinois Gastroenterology Group Project Sonar Database
Severe rectal disease, %	6.03	Illinois Gastroenterology Group Project Sonar Database
Stricture, %	22.87	Illinois Gastroenterology Group Project Sonar Database
Anatomic involvement, %	14	Illinois Gastroenterology Group Project Sonar Database
Previous GI hemorrhage, %	5	Illinois Gastroenterology Group Project Sonar Database
Previous surgery	20	Illinois Gastroenterology Group Project Sonar Database

[a] *Average weight of an US population which is 43.5% male and 42 years old*

1-3. Efficacy and safety of active treatments for Crohn's Disease

Table S6 Treatment efficacy and safety

Endpoint	5-aminosalicylates	TNF inhibitors (e.g. Infliximab)	Natalizumab	Vedolizumab	Surgery
MH resolution rate, PPPM	No evidence [6]	25.04[7]	8.34[8]	13.1[9]	4.1[10]
MH failure rate, PPPM		5.61 [11]			6.4[10]
CDAI resolution rate, PPPM	6.33[12]	28.05[13]	27.9[8]	21.9[9]	8.7[10]
CDAI failure rate, PPPM	30.7[12]	8.53[13]			2.7[10]
Infection, EPPY	62[14]	38.72[15]	215.91[16]	46.43[9]	0
Injection site reactions, EPPY	- (oral)	26.67[15]	49.92[16]	2.51[9]	0
Adverse Events, RR	1.33[12]	1	1.02[17]	0.6[18]	0
Post-surgical complications, %	0	0	0		Minor 7.4[19] major 27.8[19]
30-day re-operation, %	0	0	0		Elective 4.8, emergency 18.1[20]
30-day Mortality, %	0	0	0		Elective 1.5, emergency 8.1[20]

1-4. Model details

Comparison of monitoring modalities

One limitation of ileocolonoscopy is that it is difficult, if not impossible, to visualise the small bowel. Reporting on 153 patients who underwent ileocolonoscopy, Samuel et al. found that 67 patients had no evidence of active Crohn's Disease; 36 (53.7%) of these patients did though have active, small-bowel Crohn's Disease.[21] For this reason, ileocolonoscopy is often supplemented by magnetic resonance enterography (MRE) or computed tomographic enterography (CTE).

The PillCam Crohn's system (Medtronic Inc.), formerly named PillCam SBC, offers pan-enteric assessment of the small bowel and colon concurrently. The video capsule is swallowed by the patient and transmits images back to a recording device worn by the patient. The captured images are reviewed by the physician, with specialized software helping to identify potential Crohn's-related pathology and highlight changes from previous rounds of SBC monitoring. Passing through the whole digestive tract, SBC should allow for a more complete assessment of a patient's disease state. VCE does put the patient at minor risk of capsule retention,[22] and risk can be reduced further with use of the patency capsule.[23] Adverse events associated with ileocolonoscopy are, on the other hand, bleeding, infection, perforation, and subsequent hospital admission.[24-26]

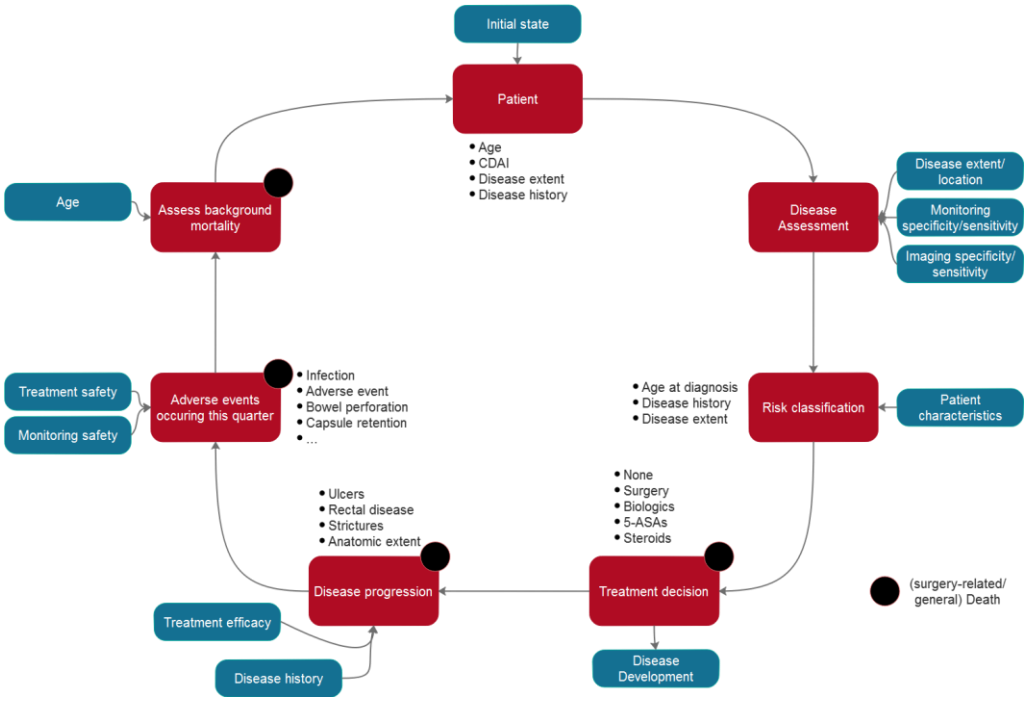
Ileocolonscopy and VCE both have high sensitivity and specificity in the identification of Crohn's Disease pathology (Table S6). Whether the small differences between monitoring modalities in terms of accuracy of diagnosis and safety profile have an impact on patient outcomes and healthcare costs is the focus of this analysis.

Decision analytic model structure

The decision analytic model was built as a discrete event simulation Figure 1 in Microsoft Excel® and conforms to good practice guidelines.[27,28] The American Gastroenterological Association patient care pathway for CD was represented by an individual patient, discrete-event simulation.[29] Each patient (N = 4,000) in the model had previously diagnosed CD and at model initiation could be in one of five disease states: *Remission* (non-active CD, non-symptomatic), *Non-active Symptomatic* (non-active CD,

but with symptomatology), *Active Symptomatic* (active CD with symptomatology), *Active Non-symptomatic* (active CD without symptomatology), or *On Treatment* (receiving medication for management of active CD). Other model states — *Treatment Failure*, *Surgery*, *Post-surgery*, and *Death* — could only be accessed after model initiation.

Figure 1 Model overview



The model starts in the "Patient" state with assignment or update of patient characteristics (e.g. age). In "Disease assessment," disease activity and extent is assessed. Based on disease assessment, a "Risk classification" is made. The "Treatment decision" is then informed by disease assessment and risk classification. If any treatment is used, its efficacy modulates "Disease progression." After disease progression, "Adverse events" related to monitoring and treatment are assessed. Lastly, mortality is assessed, which is possible in the states marked by a black circle. The red boxes are positions in the care pathway, the blue boxes are information feeding into the decision process.

Representation of Crohn's Disease

Active CD was defined by the presence of ulcers in the colon and/or small bowel. The position of ulcers is indexed using the Vienna Classification System, from proximal colon to small bowel. Different ulcer staging was supported, with severity comprising 'no ulcer', 'superficial ulcer', deep ulcer', 'abscess', and 'fistula' classifications. Ulcer progression/regression was driven by a Markov model, with a maximal two-step progression or regression every quarter. The quarterly probability of ulcer progression/regression was taken from clinical data and was modulated using treatment and the current duration of ulcer data, both of which varied by patient.

Representation of Crohn's Disease

Active CD was defined by the presence of ulcers in the colon and/or small bowel and different ulcer staging was supported, with severity comprising 'no ulcer', 'superficial ulcer', deep ulcer', 'abscess', and 'fistula' classifications. Ulcer progression/regression was driven by a Markov model, with a maximal two-step progression or regression every quarter. The probability of ulcer progression/regression was influenced by both disease and patient characteristics.

Beyond ulcers, the model tracks the development and progression of anatomic involvement, rectal disease, and strictures. The probabilities for onset and progression were modelled using mucosal healing and failure rates for the respective treatments (or no treatment) as reported by clinical studies.[6–9,30] As a simplifying assumption, anatomic involvement, rectal disease, and strictures were assumed to resolve within 6 months of ulcer resolution.

Treatments and interventions

The model supports use of four medical treatments: infliximab, natalizumab, vedolizumab, and 5-aminosalicyclic acid (5-ASA). The efficacy and safety of interventions are taken from meta-analyses.[6–9,30] Treatments increase the probability of a patient entering and remaining in remission, but also the risk of adverse events. Patients can only be prescribed one treatment for active CD at any one time, which can be switched, and high-risk patients are more likely to be prescribed biologics than are low-risk patients. The restriction to one active treatment is due to limited data on combination therapy

and model complexity. Costs for symptomatic treatments, such as pain relief and anti-diarrhoea medication, are included. In addition to medical treatments, the model includes surgical intervention, including colonic resection, fistula repair, abscess drainage, capsule removal, or emergency surgery. Surgery also comes with a risk of associated adverse events, which include mortality.

Table S7 Cost and QALY inputs

Parameter	Cost, 2016 USD	QALY
Vedolizumab, annual cost (83.6kg) **Administration, per dose**	46,304 [31] 75 [31]	-
Infliximab, annual cost **Administration, per dose**	38,122 [31] 116 [31]	-
Natalizumab, annual cost **Administration, per dose**	46,210 [32] 94 [32]	-
5-ASA, annual cost **Administration, per dose**	811 [33] -	-
Injectables, per use		-0.00014 [34]
Colonoscopy, per procedure **Physician fee, per procedure**	753 [a] 200 [a]	-0.0025 [35]
SBC, per procedure **Physician fee, per procedure**	745 [a] 196 [a]	-0.0014 [b]
MRE full costs **Physician fee, per procedure**	909 [a f] 116 [a]	-
PRIMA full costs **Physician fee, per procedure**	0 0	-
CTE full costs **Physician fee, per procedure**	348 [a] 93 [a]	-
Remission	10	0.8 [36]
Non-active symptomatic	30	0.61 [36]
Active symptomatic	50	0.5 [36]
Active non-symptomatic	20	0.8 [36]
Death	0	0
Infection	595 [c]	-0.05 [37]
Serious Infection	11,893 [38]	-0.05 [37]
Injection Site Reactions	0	-0.0001 [39]
Gastrointestinal Bleeding	22,531 [40]	-0.006 [41]
Bowel Perforation	37,573 [42]	-0.01 [41]
Capsule Retention	250 [a]	-0.0025 [35]
Surgery	51,184 [43]	-0.16 [44]

Parameter	Cost, 2016 USD	QALY
Post-surgical complications	19,232 [45]	-0.0126 [46] [e]
Adverse events	521 [47]	-0.0014 [b]
Hospitalization	4,031 [43]	-0.0014 [48]
Abscess draining	209 [a]	-0.06 [49]
Fistula repair	804 [a]	-0.03 [49]
Stricture repair	609 [a]	-0.06 [d]

5-ASA, 5-aminosalicylic acid; CTE, Computed tomography enterography; MRE, Magnetic resonance enterography; QALY, Quality adjusted life years; SBC, Small bowel and colon video capsule endoscopy. [a] *Medicare 2016, average Medicare payment amount;* [b] *Assumed half a day of QALY;* [c] *Assumed 5% of serious infection cost;* [d] *Assumed as Abscess disutility;* [e] *Assumed 9 days of hospitalization (90% percentile);* [f] *combination of two cost codes used. Costs not provided in 2016 USD were adjusted based on the healthcare producer price index.*

1-5. Sensitivity analyses

During sensitivity analyses, the variance in the results of the clinical model are explored by varying the input parameters. In each simulation, every model input (except time horizon, discount rates, and currency) was varied using a seeded-random number within the 95% confidence interval of each parameter value. Sampling used the normal distribution for all inputs, except for relative risks, which used the lognormal. A new random number was drawn for every input on every cycle, resulting in every patient having a unique care pathway. Use of a seeded-random number ensured reproducibility of results, and that the patient pathway was independent of the monitoring modality in use. From individual patient results, new subpopulations were created by bootstrapping (sampling with replacement). For the budget-impact analysis, bootstrapping was performed 1,000 times with populations of 750 patients and in the cost-effectiveness analysis, bootstrapping was performed 2,000 times with populations of varying sizes.

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