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Biologics versus Immunomodulators or Antibiotics for the Management of Fistulizing Crohn's Disease: A Review of Comparative Clinical Effectiveness and Cost-Effectiveness

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Abbreviations

ALB	albumin
BMI	body mass index
CDAI	Crohn's Disease Activity Index
CRP	C-reactive protein
SES-CD	Simple Endoscopic Score for Crohn's Disease
EE	economic evaluation
ESR	erythrocyte sedimentation rate
IBD	inflammatory bowel disease
ICER	incremental cost-effectiveness ratio
NRS	non-randomized study
PPP	purchasing power parity
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	quality-adjusted life year
RCT	randomized controlled trial
SR	systematic review

Context and Policy Issues

Crohn's disease is a chronic inflammatory condition of the gastrointestinal tract. A number of complex variables, including genetic susceptibility, environmental factors, and intestinal microflora, are thought to contribute to the development of Crohn's disease.[1] Disease progression typically occurs through alternating periods of relapse (flare-ups) and remission, eventually leading to severe bowel damage.[1] Symptoms of Crohn's disease include abdominal pain, chronic diarrhea, fever, weight loss, fatigue, rectal bleeding, and anorexia.[1,2]

The incidence and prevalence of Crohn's disease (and other inflammatory bowel diseases) is increasing worldwide.[3] A 2012 systematic review estimated the prevalence of Crohn's disease to be as high as 319 per 100,000 people in North America.[4] Approximately one-third of patients diagnosed with Crohn's disease will develop fistulas throughout the course of their disease.[5] Fistulas are abnormal, tunnel-like connections between two epithelial surfaces (e.g., bowel lumen and skin) that can cause pain, infection, and fecal seepage.[6,7] Although much of the pathogenesis of fistulas is only partially understood, current research implicates epithelial-to-mesenchymal transition as the driving force for fistula development.[5]

Treatment strategies for fistulizing Crohn's disease aim to control infection and sepsis, promote healing of the mucosal and fistula tracts, and improve patients' health-related quality of life.[6,8] Non-biologic treatments for fistulizing Crohn's disease include antibiotics (e.g., ciprofloxacin, metronidazole), immunosuppressants (e.g., methotrexate, thiopurines, aminosalicylates), and surgical interventions (e.g., fibrin glue, fistula plugs, fistulotomy, fistulectomy, placement of setons, stoma, colectomy, proctectomy).[6,8] In addition to these conventional therapies, a number of biologics have been developed for the treatment of Crohn's disease over the last two decades. Biologics are antibodies designed to precisely target specific proteins involved in the immune process, inhibiting inflammation and interfering with disease progression. The biologics used to treat fistulizing Crohn's disease include tumor necrosis factor-α inhibitors (e.g., infliximab, adalimumab, golimumab) and anti-integrin $\alpha_4\beta_7$ agents (e.g., vedolizumab).[9]

Individuals diagnosed with Crohn's disease have traditionally received initial treatment with non-biologic medications.[10] As the disease progression occurs they would then be "stepped-up" to biologics.[10] As the volume of literature supporting the use of biologics expands it is unclear if this care pathway is supported by the evidence.

This report is part of a series of reviews CADTH is conducting on the effectiveness of treatment strategies for patients with inflammatory bowel disease (both Crohn's disease and ulcerative colitis).[11-14] The purpose of the current report is to evaluate the clinical and cost-effectiveness of biologics (i.e., adalimumab, infliximab, and vedolizumab) compared with immunomodulators or antibiotics for the management of fistulizing Crohn's disease.

Research Questions

1. What is the comparative clinical effectiveness of biologics (with or without concomitant immunomodulators or antibiotics) compared with immunomodulators or antibiotics for the management of fistulizing Crohn's disease?
2. What is the cost-effectiveness of biologics (with or without concomitant immunomodulators) compared with immunomodulators or antibiotics for the management of fistulizing Crohn's disease?

Key Findings

Three relevant systematic reviews, one randomized controlled trial, and one economic evaluation were identified regarding the clinical and cost-effectiveness of biologics compared with immunomodulators or antibiotics for the management of fistulizing Crohn's disease.

Evidence of limited quality from one randomized controlled trial suggested that treatment with infliximab is likely effective for improving measures of Crohn's disease activity and fistula status compared to treatment with conventional therapy (azathioprine and methylprednisolone) following 30 weeks of treatment.

Three systematic reviews of economic studies (that included two unique relevant primary studies) and one additional economic evaluation reported mixed findings on the cost-effectiveness of biologics versus immunomodulators or antibiotics for the management of fistulizing Crohn's disease. Two of the primary studies concluded that biologics were cost-effective compared to various non-biologic treatments; however, one primary study suggested that infliximab was not cost-effective compared to treatment with 6-mercaptopurine and metronidazole.

Given the limited availability of relevant literature and the methodological limitations of the reviewed studies (e.g., lack of blinding, the low number of included participants), the effectiveness of biologics compared with immunomodulators or antibiotics for the treatment of fistulizing Crohn's disease remains uncertain.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including Ovid Medline, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and economic studies. Where possible, retrieval was limited to the human population. The

search was also limited to English language documents published between January 1, 2009 and February 14, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult and pediatric patients with fistulizing Crohn's disease
Intervention	Biologics: adalimumab, infliximab, or vedolizumab (administered with or without immunomodulators [e.g., azathioprine, 6-mercaptopurine] or antibiotics [e.g., ciprofloxacin, metronidazole])
Comparator	Antibiotics (e.g., ciprofloxacin, metronidazole) Immunomodulators (e.g., azathioprine, 6-mercaptopurine)
Outcomes	Q1. Response based on commonly accepted disease activity scales such as Crohn's Disease Activity Index (CDAI) or the Harvey–Bradshaw Index, clinical response rate, primary non-response, secondary loss of response, deep remission, fistula improvement/resolution/closure, need for surgery, hospitalization, mortality, quality of life, safety outcomes (harms including adverse events, serious adverse events, infections and malignancies, discontinuation, adverse events, serious adverse events, complications due to being hospitalized [e.g. hospital-acquired infections like C. difficile/MRSA]), development of anti-drug antibodies Q2. Cost-effectiveness
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and economic evaluations

MRSA = methicillin-resistant *Staphylococcus aureus*.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2009. Primary studies retrieved by the search were excluded if they were captured in one or more included systematic reviews.

Systematic reviews that had inclusion criteria more broad than that of our review were examined in detail to ascertain whether data could be extracted from a relevant sub-set of included studies, rather than excluding the systematic review entirely. If we were unable to identify relevant studies upon detailed investigation the systematic review was excluded.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised by one reviewer using AMSTAR II,[15] clinical studies were critically appraised using the Downs and Black checklist,[16] and economic studies were assessed using the Drummond checklist.[17] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

Summary of Evidence

Quantity of Research Available

A total of 874 citations were identified in the literature search. Following screening of titles and abstracts, 795 citations were excluded and 79 potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search for full-text review. Of these 81 potentially relevant articles, 76 publications were excluded for various reasons, while five publications met the inclusion criteria and were included in this report. These comprised three systematic reviews,[18-20] one randomized controlled trial (RCT),[21] and one economic evaluation.[22] Appendix 1 presents the PRISMA[23] flowchart of the study selection.

Additional references of potential interest are provided in Appendix 6.

Summary of Study Characteristics

Three systematic reviews,[18-20] one RCT,[21] and one economic evaluation[22] were identified and included in this review. No relevant health technology assessments, meta-analyses, or non-randomized studies were identified. Study characteristics were extracted by one reviewer and are summarized below. Detailed characteristics are available in Appendix 2, Tables 2 to 4.

Study Design

All three systematic reviews[18-20] had objectives and inclusion criteria that were broader than our report; only information from studies relevant for our report is included here (i.e., studies on the comparative effectiveness of biologics versus with immunomodulators or antibiotics for fistulizing Crohn's disease). The review by Pillai et al.[18] searched for primary economic evaluations published before March 21, 2017. The second systematic review[19] included cost-utility analyses (with or without the use of modeling) published up to June 2014. The Tang et al.[20] review searched for cost studies, economic evaluations, and systematic or narrative reviews related to economic evaluations published up to June 2012. The total number of studies included in these systematic reviews ranged between 25 and 49; however, all three reviews included and summarized two primary studies[24,25] that are relevant under our inclusion criteria. The relevant primary study overlap between these systematic reviews is summarized in Appendix 5, Table 11.

The included RCT[21] recruited participants from a single centre in China between December 2012 and September 2015. The study was open-label.

The included economic evaluation[22] analyzed the cost-effectiveness of different biological sequences for fistulizing Crohn's disease in various European countries using a seven state Markov model. The clinical and cost inputs used in these models came from several clinical studies, as selected by the authors. Country specific drug costs were informed by official price lists. The model was conducted from the third-party payer perspective and used a five year time horizon.

Year of Publication and Country of Origin

The included systematic reviews were by authors in Switzerland,[18] Finland,[19] and the United States.[20] They were published in 2017,[18] 2015,[19] and 2013.[20] The relevant primary studies included in the systematic reviews were published in 2008[25] and 2001[24] from authors in the United Kingdom and the United States, respectively.

The included RCT[21] was conducted in China and was published in 2016.

The first author on the economic evaluation[22] was based in Hungary; however, the model provided cost-effectiveness estimates for nine European countries (Belgium, France, Germany, Hungary, Italy, Spain, Sweden, the Netherlands, and the UK). This study was published in 2018.

Patient Population

One systematic review[18] included primary studies that included adults (≥18 years of age) diagnosed with inflammatory bowel disease (both Crohn's disease and ulcerative colitis). The review by Huoponen et al.[19] included studies with patients (≥ 16 years of age) diagnosed with moderate-to-severe Crohn's disease or ulcerative colitis. The third systematic review[20] included studies with patients (of any age) diagnosed with moderate-to-severe Crohn's disease. Only primary studies in populations with fistulizing Crohn's disease were considered relevant for our review. One relevant primary study[24] from the systematic reviews included treatment-naïve adults with Crohn's disease who were symptomatic with perianal fistulas. The second relevant primary study[25] included participants (of unspecified age) who were diagnosed with fistulizing Crohn's disease.

The RCT conducted by Wu et al.[21] recruited adults (≥18 years of age) with Crohn's disease complicated with intestinal fistulas who were diagnosed by clinical, endoscopic, histopathological, and radiological examinations. A total of 42 participants were included in the study. The mean age of participants was 31.9 years and the proportion of male participants was 59.5%. Recruited participants had a mean Crohn's Disease Activity Index (CDAI) score of 317.4 at baseline.

The Baji et al.[22] economic evaluation was constructed for patients with active fistulizing Crohn's disease who had single or multiple draining abdominal and/or perianal fistulas at baseline and who had not responded to conventional treatment (including antibiotics, drainage, and immunosuppressive therapy). The authors assumed patients had a mean age of 40 years and a mean weight of 65 kg.

None of the included studies[18-22,24,25] studies aimed to evaluate the use of biologics for the management of fistulizing Crohn's disease in children (<18 years of age).

Interventions and Comparators

Three systematic reviews[18-20] included primary studies that compared pharmacological and surgical interventions for the treatment of inflammatory bowel diseases. All three reviews[18-20] identified and included two primary studies[24,25] relevant to our report. The primary study by Arsenau et al.[24] compared three different infliximab (5 mg/kg) treatment strategies to a combination of 6-mercaptopurine and metronidazole. The Lindsay et al.[25] study compared treatment with infliximab (5 mg/kg; given at weeks 0, 2, 6, and every 8 weeks thereafter) to standard care, which consisted of immunomodulators and/or corticosteroids.

The identified RCT[21] compared infliximab, given intravenously over the course of 32 weeks (5 mg/kg at 0, 2, and 6 weeks followed by once every 8 weeks), to conventional treatment. Patients allocated to the conventional treatment arm received methylprednisolone and azathioprine (1.5–2.5 mg/kg/day) for 32 weeks. All study participants also received enteral nutrition by nasogastric tube every night for 2 months (1,000 kcal/night), regardless of their treatment assignment. The authors also noted that patients with complex fistula from both

groups were treated with incision and drainage of abscess, side-to-side anastomosis, and antibiotics.

The economic evaluation by Baji et al.[22] compared several biological treatment strategies (infliximab, biosimilar-infliximab, adalimumab, vedolizumab) with standard, non-biological care consisting of sulfasalazine (2,000 mg/day) and prednisolone (20 mg/day).

None of the included studies[18-22,24,25] directly compared biologics to antibiotics alone for the treatment of individuals with fistulizing Crohn's disease.

Outcomes

Three systematic reviews[18-20] summarized cost-effectiveness data from their included studies. Outcomes of interest included the nominal costs of treatment strategies,[18] quality-adjusted life year (QALY) values,[18] and incremental cost-effectiveness ratios (ICERs).[18-20]

It is important to note that the two relevant primary studies[24,25] summarized from the three systematic reviews[18-20] likely examined additional outcomes that were not discussed within the systematic reviews. It is typical for systematic reviews to consolidate data on primary outcomes or a specific outcome of interest (in this case QALYs and ICERs), rather than completely summarizing all findings from primary studies.

The RCT by Wu et al.[21] assessed several clinical outcomes, including CDAI scores, Simple Endoscopic Score for Crohn's Disease (SES-CD), the proportion of patients who experienced fistula healing, and adverse events. The CDAI is a validated tool used to characterize the severity of Crohn's disease.[26-29] A score of less than 150 would typically indicate clinical remission, while a score of greater than 450 is a marker of severe Crohn's disease (total range is 0 to 1100).[26] The SES-CD is a validated scale that scores four items (i.e., ulcer size, proportion of the surface area that is ulcerated, proportion of the surface area affected, and stenosis) on a scale from 0 to 3 for five segments of the gastrointestinal tract (i.e., ileum, right colon, transverse colon, left colon, and rectum).[30] Total scores range between 0 and 56, with a higher score indicating more severe disease.[31] Additionally, several laboratory indicators were monitored throughout the study, including erythrocyte sedimentation rate (ESR; mm/h), C-reactive protein (CRP; mg/L), body mass index (BMI; kg/m^2) and albumin (ALB; g/L).

The included economic evaluation[22] estimated the cost-effectiveness of various biologic treatments from a third-party payer perspective using ICERs (i.e., change in QALYs divided by the difference in treatment costs).

Summary of Critical Appraisal

Critical appraisal of the included studies is summarized below and detailed in Appendix 3, Tables 5 to 7.

Systematic Reviews

The strengths and limitations of the included systematic reviews[18-20] were assessed using the AMSTAR II tool.[15]

The three systematic reviews[18-20] clearly stated their objectives and inclusion criteria, provided key search terms and search strategy, described the article selection process, provided a list of included studies and summarized their characteristics, and conducted quality assessment of included studies. The reviews[18-20] included flow charts illustrating

study selection and provided reasons for article exclusion. Additionally, the Huoponen et al.[19] review included a list of excluded studies. These strengths of reporting increase confidence in the findings and the reproducibility of the systematic reviews. While the review by Pilllai et al.[18] contained an explicit statement that the review methods were established prior to conducting the review, it was unclear whether the methods used in the other two systematic reviews[19,20] were established a priori as none they made no reference to a study protocol. Multiple databases were used across all studies;[18-20] however, two of the systematic reviews[18,20] did not conduct a grey literature search, increasing the risk for missing relevant, non-indexed studies. All three reviews[18-20] restricted their search by only including studies published in English. None of the authors provided justification for this decision. Study selection and data extraction were performed individually by multiple authors followed by group discussion of results in the Tang et al.[20] review, decreasing likelihood for inconsistency in these processes. The other two systematic reviews[18,19] did not perform study selection, data extraction, or quality assessment in duplicate, increasing the risk for errors in these processes. All three systematic reviews[18-20] included no discussion on the possibility of publication bias; therefore it is unclear how this bias may have influenced the findings. The authors of all three systematic reviews[18-20] disclosed their conflicts of interest and their sources of funding, none of which were considered likely to have influenced their findings.

RCTs

The strengths and limitations of the included RCT[21] were assessed using the Downs and Black checklist.[16]

The included RCT[21] had clearly described objectives, interventions, controls, main outcomes, inclusion/exclusion criteria, and patient recruitment methodology. Randomization appears to have been done using an appropriate technique; however, there was little information provided on the specific methodology, increasing the risk for a biased allocation process (selection bias). The study included no mention of sample size calculations and recruited a relatively low total number of participants (N = 44). As a result the study may have been not had enough power to detect a statistically meaningful difference for several outcomes of interest. It is unclear if study participants and outcome assessors were aware of their allocation to study arms (open-label), creating a risk for bias in either direction depending on the perceptions and expectations of participants and outcome assessors. Baseline patient characteristics, which included age, sex, mean CDAI score, duration of disease, lesion site, and disease behavior, were clearly described and were found to have no statistically significant between-group differences at baseline (increasing confidence in the randomization processes). The length of follow-up was consistent between the treatment and control groups (14 weeks and 30 weeks after treatment initiation) and no patients were lost to follow-up.

Study participants, care providers, and health care settings that appear to be representative of the "real-world", increasing the external validity of the study. However, this study was conducted at a single centre in China, and the generalizability of the findings to other centres or countries is not clear. The authors of the RCT[21] stated they had no conflicts of interest and disclosed their sources of funding, none of which were considered likely to have influenced their findings.

Economic Evaluations

The strengths and limitations of the included economic evaluation[22] were assessed using the Drummond checklist.[17]

The research objectives, economic importance of the research question, time horizons, viewpoints of the analysis, and rationale for choosing alternative interventions compared were clearly stated. The five year time horizon appears to be appropriate for examining the cost-effectiveness of treatment strategies for fistulizing Crohn's disease. Additionally, the choice of form of economic evaluation (a seven-state Markov model) was justified. These methodological strengths increase confidence in the findings of the study.

As for the methods of data collection, the sources of drugs costs (all of which were reported in 2015 euros, €), health utility states, and probabilities for transitioning between model states were included. Each source of data was graded with a risk of bias, providing an estimate of their validity. The country-specific discount rates used in the model were clearly stated; however, it is unclear why these were selected. The authors included a one-way sensitivity analysis for a number of variables, providing estimates of how uncertainty in the model inputs may affect the cost-effectiveness results. Because this study was conducted using European data, it is unclear how the findings would apply to the Canadian setting.

The authors of the included economic evaluation[22] disclosed a series of financial ties with various pharmaceutical companies, including Hospira, Pfizer, Sager Pharma, Egis Pharma, Abbott Laboratories, Merck & Co., AbbVie, Warner Chilcott, Ferring, Falk Pharma, Celgene, Roche, Johnson and Johnson, Cosmo Pharmaceuticals, Vifor, and Novo Nordisk, among many others. In addition, the study was directly funded by an unrestricted grant from Pfizer Hospira UK. These conflicts of interest may be seen as limitations.

Summary of Findings

The overall findings of the included literature are summarized below. A detailed summary of the main findings and authors' conclusions are available in Appendix 4, Tables 8 to 10.

Clinical Effectiveness of Biologics Compared with Immunomodulators or Antibiotics for Fistulizing Crohn's Disease

Measures of Disease Activity

Evidence regarding the comparative effectiveness of biologics versus immunomodulators for disease activity was available from one RCT.[21] This study randomized individuals with fistulizing Crohn's disease to receive infliximab or conventional therapy (azathioprine and methylprednisolone). The results suggested that participants treated with infliximab demonstrated statistically significant ($P < 0.05$) improvements in CDAI and SES-CD scores compared to those in the conventional therapy group following 30 weeks of treatment. Mean CDAI scores were 125.6 and 178.6 for participants in the infliximab and conventional therapy groups, respectively. Although not directly discussed by the study authors, a CDAI score of less than 150 would typically indicate clinical remission.[26]

Fistula Healing

The comparative effectiveness of biologics versus immunomodulators for fistula healing was available from one RCT.[21] This study defined a case of healing as complete response and closing of the fistula. Compared with participants treated with conventional therapy (azathioprine and methylprednisolone), those who were in the infliximab group were

statistically significantly ($P < 0.05$) more likely to experience fistula healing following 30 weeks of treatment. The proportion of patients who had fistula healing were 90.0% and 27.3% in the infliximab and conventional therapy groups, respectively.

Laboratory Indicators

One RCT[21] evaluated the comparative effectiveness of biologics versus immunomodulators with respect to various laboratory indicators. The authors measured and monitored albumin concentration, body mass index, C-reactive protein concentration, and erythrocyte sedimentation rate in patients with fistulizing Crohn's disease randomized to receive infliximab or conventional therapy (azathioprine and methylprednisolone). There were no statistically significant differences between treatment groups for any of these indicators throughout the study (actual *P*-values values were not reported in the publication).

Cost-Effectiveness of Biologics Compared with Immunomodulators or Antibiotics for Fistulizing Crohn's Disease

Incremental Cost-Effectiveness Ratios

Evidence regarding the comparative cost-effectiveness of biologics versus immunomodulators or antibiotics using ICERs was available from three systematic reviews[18-20] and one economic evaluation.[22]

All three systematic reviews[18-20] summarized data from two relevant primary studies.[24,25] The study by Arsenau et al.[24] compared three different infliximab treatment strategies to standard care (6-mercaptopurine and metronidazole) using a Markov model. As reported in the Tang et al. review (which did not adjust for currency inflation), the ICERs of these infliximab treatment strategies were $355,450, $360,900, $377,000 per QALY (in 1999 United States dollars). The Pillai et al.[18] systematic review adjusted ICERs to reflect 2015 purchasing power parity (PPP), resulting in ICERs for the infliximab treatment strategies of 505,796.84 PPP, 513,552.06 PPP, and 536,461.97 PPP per QALY compared to standard care. The Huoponen et al.[19] review adjusted costs to 2014 euros, resulting in ICERs of €438,617, €445,477, and €465,394 per QALY for the three infliximab treatment strategies. The second primary study[25] evaluated the cost-effectiveness of infliximab initial infusions and maintenance treatment versus standard care (immunomodulators and/or corticosteroids) using a Markov model. The Tang et al.[20] review, which presented the findings in the same currency as the primary study, reported an ICER of £29,752 per QALY (denoted in 2005/2006 British pounds). The two other systematic reviews[18,19] reported infliximab treatment ICERs of 48,751.83 PPP and €51,397 per QALY versus standard care following adjusting to 2015 PPP and 2014 euros, respectively. The authors of the primary study[25] considered their findings to indicate cost-effectiveness based on the £30,000 willingness to pay threshold set by the National Institute for Health and Care Excellence (NICE); however, these ICERs were at or above some of the willingness-to-pay thresholds proposed in the systematic reviews.[18-20]

The identified economic evaluation[22] investigated the cost-effectiveness of biological treatment sequences for fistulizing Crohn's disease across Europe using a Markov model-based analysis. The findings indicated that biosimilar-infliximab was the most cost-effective treatment against standard care (sulfasalazine and prednisolone) across the nine European countries. The ICERs for biosimilar-infliximab ranged between €34,684 and €72,551 per QALY in the base case analysis (reported in 2015 euros). The next most cost-effective treatment was infliximab, followed by adalimumab and then vedolizumab.

Limitations

A number of limitations were identified in the critical appraisal (Appendix 3, Tables 5 to 7), however, additional limitations exist.

The quantity of identified relevant literature was relatively low. The clinical effectiveness findings are drawn from a single RCT.[21] Similarly, the cost-effectiveness findings are from three systematic reviews[18-20] and one additional economic evaluation.[22] The systematic reviews included a total of two unique relevant primary studies that were published in 2008 and 2001.[24,25] As a result, these two economic analyses do not incorporate any clinical data published since 2008 and may use outdated sources for pricing drugs and associated costs. The scarcity of comparative evidence found in this report is consistent with a number of systematic reviews that identified no such studies despite broad search methodologies and timeframes.[6,8,32-36]

None of the included studies[18-22] contained information specific to pediatric populations with fistulizing Crohn's disease; thus, the comparative clinical and cost-effectiveness of biologics versus immunomodulators or biologics in children is unknown.

The RCT[21] included treatment arms with a limited number of participants (< 25). It is clear from the data that these small groups hindered the ability of the study to detect a statistically significant difference for several monitored outcomes.

The applicability of the evidence base to Canadian settings is unclear as all relevant primary studies[21,22,24,25] were conducted outside of Canada (only one was conducted in North America);[24] however, there is no strong evidence suggesting that the clinical effectiveness results would not generalize to Canadians with fistulizing Crohn's disease. There is higher uncertainty around the generalizability of the cost-effectiveness findings due to the potential for significant differences in drug prices and associated costs between Canada and the countries in which the primary studies took place.

As outlined in our inclusion criteria, only studies that directly compared biologics and immunomodulators or antibiotics for the treatment of fistulizing Crohn's disease were included in this report. Although the potential benefit of these drugs versus other comparators (e.g., placebo, no treatment, surgery) is outside of the scope of this report, there are a number of recent systematic reviews that used a more wide-ranging lens to review the literature on fistulizing Crohn's disease.[6,8,32,35]

Conclusions and Implications for Decision or Policy Making

This review was comprised of three systematic reviews of economic evalutions,[18-20] one RCT,[21] and one economic evaluation.[22]

Evidence from one RCT[21] suggested that infliximab was more effective than conventional therapy (azathioprine and methylprednisolone) for the treatment of fistulizing Crohn's disease. Participants who were treated with infliximab demonstrated statistically significant improvements in measures of disease activity (CDAI and SES-CD scores) and in fistula status compared to those treated with conventional therapy (azathioprine and methylprednisolone) following 30 weeks of treatment.

The conclusions of the identified economic studies[18-20,22,24,25] were not consistent regarding the comparative cost-effectiveness of biologics versus immunomodulators or antibiotics. Two primary studies[22,25] concluded that biologics were cost-effective compared to various

standard care treatments; however, one primary study[24] suggested that infliximab was not cost-effective compared to treatment with 6-mercaptopurine and metronidazole.

The limitations of the included studies and of this report should be considered when interpreting the results. The findings highlighted in this review come with a high degree of uncertainty. Further research investigating the comparative clinical and cost-effectiveness of biologics versus immunomodulators or antibiotics, especially through the use of large, methodologically-sound RCTs, would help reduce this uncertainty.

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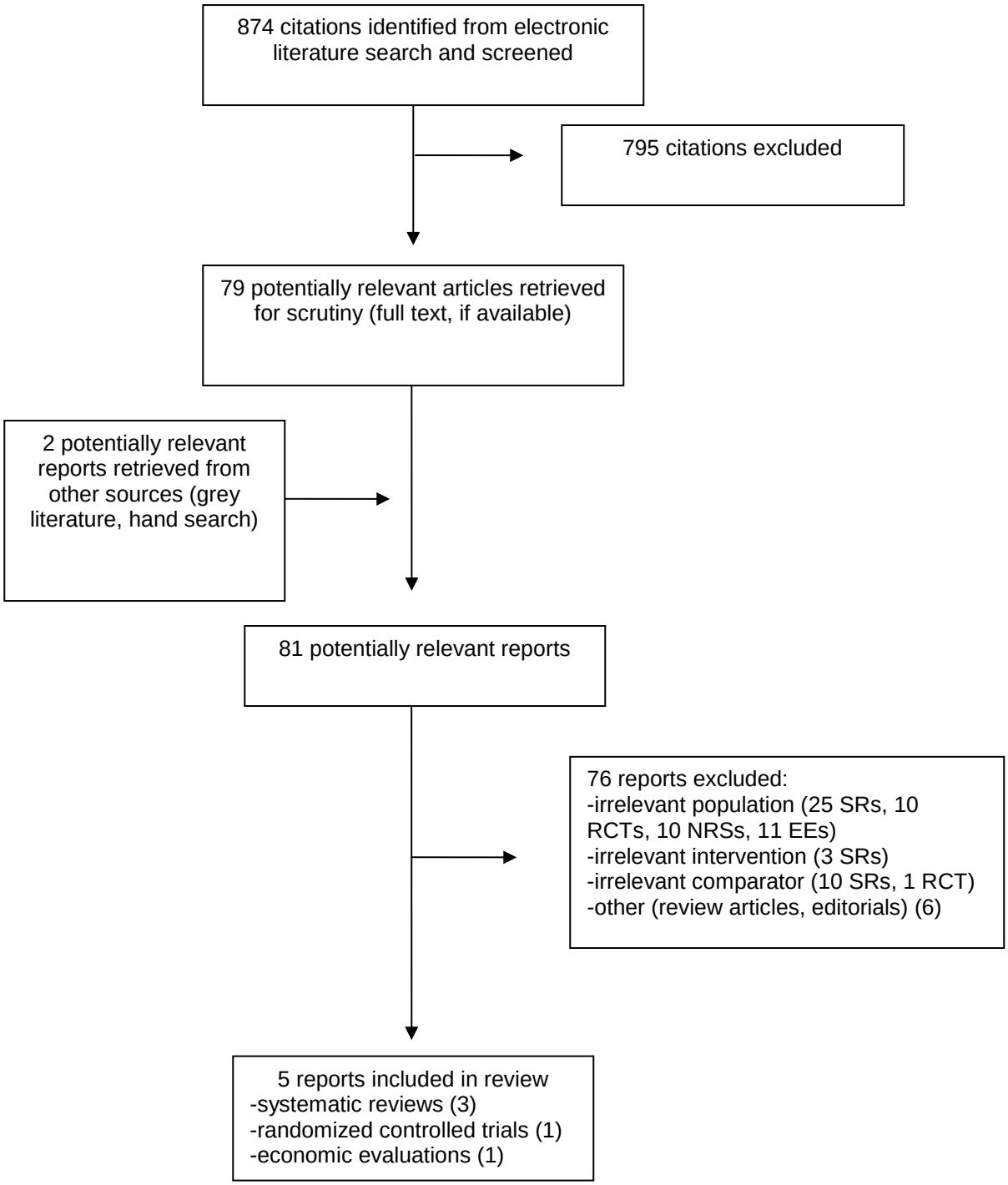
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews

First Author, Publication Year, Country	Study Designs, Search Strategy, Numbers of Studies Included, Quality Assessment Tool, and Objective	Population Characteristics	Intervention and Comparator(s)	Outcomes, Length of Follow-Up
Pillai, 2017[18] Switzerland	**Study design**: SR of economic evaluations **Literature search strategy**: An electronic search was conducted to identify studies published before 16 November 2016 using several databases, including Ovid Medline, Embase, Database of Abstracts of Reviews of Effects, National Health Service Economic Evaluation Database, and Health Technology Assessment Database. The initial search was updated on 21 March 2017, and was supplemented by a manual search of references from identified literature **Number of studies included**: In total, 49 primary economic evaluations were included, with 2 relevant for our report[24,25] **Quality assessment tool**: Conducted using the Drummond checklist for economic evaluations and Philips' checklist[37] for model-based economic evaluations **Objective**: "to provide an understanding of the cost-effective treatment strategies, particularly the biologic agents, and identify gaps in the literature and requirements for future economic models in IBD."[18] (*p*2-3)	Adults (≥18 years of age) diagnosed with CD or UC (only information on patients with fistulizing CD was included in our review).	Pharmacological and surgical interventions for the treatment of IBD (including biologics, immunomodulators, and antibiotics). Studies relevant to our report used infliximab, 6-mercaptopurine, metronidazole, and standard care (immunomodulators and/or corticosteroids) as interventions and comparators of interest.	**Outcome measures searched in the SR:** - Costs associated with treatments - QALYs - ICERs **Follow-up:** NR
Huoponen, 2015[19] Finland	**Study design**: SR of cost-utility analyses (with or without the use of economic modeling) **Literature search strategy**: Authors performed a comprehensive literature search using Ovid Medline, Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, Cochrane Methodology	Patients (≥ 16 years of age) diagnosed with moderate-to-severe CD or UC (only information on patients with fistulizing CD was included in our review).	**Interventions**: Biological treatment alone or in combination with conventional treatment or surgery **Comparators**: Conventional treatment, surgery, biological treatment, or placebo	**Outcome measures searched in the SR:** - QALYs - ICERs **Follow-up:** Search criteria required that the time horizon was ≥ 12 months

Table 2: Characteristics of Included Systematic Reviews

First Author, Publication Year, Country	Study Designs, Search Strategy, Numbers of Studies Included, Quality Assessment Tool, and Objective	Population Characteristics	Intervention and Comparator(s)	Outcomes, Length of Follow-Up
	Register, Heath Technology Assessment Database, and NHS Economic Evaluation Database), and SCOPUS (including Embase) in June 2014. The search was supplemented by a manual search of references from identified literature and a grey literature search using and other relevant websites and databases (Centre for Reviews and Dissemination, Current Controlled Trials, ClinicalTrials.gov, and PROSPERO) **Number of studies included**: In total, 25 studies were included, with 2 relevant for this review[24,25] **Quality assessment tool**: All included studies were assessed using the Drummond checklist[17] and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines.[38] Economic evaluations that used modeling methods were assessed using Philips' checklist.[37] **Objective**: "to evaluate existing relevant evidence regarding the cost-effectiveness of biologics for the treatment of IBDs."[19] (*p*3)		Studies relevant to our report used infliximab, 6-mercaptopurine, metronidazole, and standard care (immunomodulators and/or corticosteroids) as interventions and comparators of interest.	
Tang, 2013[20] United States	**Study design**: SR of cost studies, economic evaluations, or systematic or narrative reviews related to economic evaluations **Literature search strategy**: A comprehensive literature search was conducted in June 2011 and updated in June 2012. Articles published between January 1995 and June 2012 were searched for in PubMed, EMBASE, ABI/INFORM, Tuft's Cost-Effectiveness Analysis Registry Database, Cochrane National Health Service Economic Evaluation Database, International Pharmaceutical Abstracts, Web of Science, and Google Scholar. The search was	Patients (of any age) diagnosed with moderate-to-severe CD (only information on patients with fistulizing CD was included in our review).	**Interventions**: Biological treatments for CD (infliximab, adalimumab, certolizumab pegol, and natalizumab) **Comparators**: Standard care, including 5-aminosalicylic acid and its derivatives, corticosteroids, immunosuppressants, antibiotics, and surgical interventions Studies relevant to our report	**Outcome measures searched in the SR:** - Costs associated with biological treatments - Cost-effectiveness measures (e.g., ICERs) **Follow-up:** NR

Table 2: Characteristics of Included Systematic Reviews

First Author, Publication Year, Country	Study Designs, Search Strategy, Numbers of Studies Included, Quality Assessment Tool, and Objective	Population Characteristics	Intervention and Comparator(s)	Outcomes, Length of Follow-Up
	supplemented by a manual search of references from obtained studies **Number of studies included**: In total, 38 studies were included, with 2 relevant for our report[24,25] **Quality assessment tool**: Conducted using the Drummond checklist[17] **Objective**: "to systematically review the current literature on economic studies that evaluated biological agents, specifically, infliximab, adalimumab, certolizumab pegol, and natalizumab, when used in the treatment of moderate-to-severe CD."[20] (*p*2674)		used infliximab, 6-mercaptopurine, metronidazole, and standard care (immunomodulators and/or corticosteroids) as interventions and comparators of interest.	

CD = Crohn's disease; IBD = inflammatory bowel disease; ICER = incremental cost-effectiveness ratio; NR = not reported; QALY = quality-adjusted life year; RCT = randomized controlled trial; SR = systematic review; UC = ulcerative colitis.

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design, Setting, and Objective	Patient Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Wu, 2016[21] China	**Study design**: Open-label, single-centre RCT **Setting**: Participants were recruited from the First Affiliated Hospital of Wenzhou Medical University, Zhejiang Province, Southeast China, between December 2012 and September 2015 **Objective**: To investigate the potential application of enteral nutrition in CD patients with intestinal fistulas undergoing infliximab treatment or conventional therapy	Adults (≥18 years of age) with CD complicated with intestinal fistulas who were diagnosed by clinical, endoscopic, histopathological, and radiological examinations. **Number of patients**: 42 (20 in the infliximab group; 22 in the conventional therapy group) **Mean age**: 31.6 ± 11.7 years in the infliximab group; 32.1 ± 11.8 years in the conventional therapy group **Sex**: 60% male in the infliximab group; 59% male in the conventional therapy group **Mean CDAI score**: 325.6 ± 70.8 in the infliximab group; 309.9 ± 69.3 in the conventional therapy group	**Intervention**: Infliximab treatment given intravenously over the course of 32 weeks (5 mg/kg at 0, 2, and 6 weeks followed by once every 8 weeks) **Comparator**: Conventional treatment consisting of methylprednisolone and azathioprine (1.5–2.5 mg/kg/day) for 32 weeks All patients received enteral nutrition by nasogastric tube every night for 2 months (1,000 kcal/night). Patients with complex fistula from both groups were treated with incision and drainage of abscess, side-to-side anastomosis, and antibiotics.	**Outcomes**: - Various laboratory indicators, including ESR, CRP, and ALB levels - BMI - CDAI scores - Endoscopy examination (SES-CD) - Fistula healing - Adverse events **Follow-up**: outcomes were assessed at 14 and 30 weeks after treatment initiation

ALB = albumin; BMI = body mass index; CD = Crohn's disease; CDAI = Crohn's disease activity index; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; RCT = randomized controlled trial; SES-CD = Crohn's disease simplified endoscopic score.

Table 4: Characteristics of Included Economic Evaluations

First Author, Publication Year, Country	Type of Analysis, Approach, Time Horizon, Perspective	Decision Problem	Population Characteristics	Intervention and Comparator(s)	Clinical and Cost Data Used in Analysis	Main Assumptions
Baji, 2018[22] Hungary	**Analysis:** Cost-effectiveness analysis using a 7 state Markov model. The model ran in 3-month cycles **Approach**: Model-based **Time horizon:** 5 years **Perspective:** Third-party payer's perspective	"to analyse the cost-effectiveness of the different treatment sequences with available biologicals (IFX, bsIFX, ADA, VEDO), for the treatment of fistulising CD in nine European countries, namely in Belgium, France, Germany, Hungary, Italy, Spain, Sweden, the Netherlands and the UK."[22] (*p*311)	Patients with active fistulizing CD who had single or multiple draining abdominal and/or perianal fistulas at baseline, who had not responded to conventional treatment (including antibiotics, drainage and immunosuppressive therapy), and were eligible for biological treatment. **Mean age**: The model assumed a mean age of 40 years **Sex**: NR 7 state Markov model: 1. Initiation of biologic therapy 2. Complete fistula healing 3. Incomplete fistula healing 4. Biologic therapy refractory 5. Surgery 6. Post-surgery remission 7. Death	**Intervention**: Biological treatments (IFX, bsIFX, ADA, VEDO) for CD **Comparator**: Standard (non-biological) care (sulfasalazine, 2,000 mg/day and prednisolone, 20 mg/day)	- Drug costs (official list prices with various discounts applied) - Drug administration costs - Non-surgical hospitalization costs - Health utility values for each model state	- The transition probabilities between model states were estimated using evidence of varying quality - The risks for mortality were assumed to be different depending on health state - The probability of moving from the incomplete healing state to the complete healing state is 0 (due to the lack of data) - The efficacy of the 2nd and 3rd biological treatment will decrease by 10% regardless of the agent - One analysis assumed that official list prices of biologics were up to 30% higher than the real prices (which were not publically available)

ADA = adalimumab; bsIFX = biosimilar-infliximab; CD = Crohn's disease; IFX = infliximab; NR = not reported; VEDO = vedolizumab.

Appendix 3: Critical Appraisal of Included Publications

Table 5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR II[15]

Strengths	Limitations
Pillai, 2017[18]	
• The objectives and inclusion/exclusion criteria were clearly stated and included components of population, intervention, comparator, and outcomes • Multiple databases were searched (Ovid Medline, Embase, Database of Abstracts of Reviews of Effects, National Health Service Economic Evaluation Database, and Health Technology Assessment Database). In addition, a manual search of references from identified literature was performed • Search terms and dates were provided (November 16, 2016, updated on March 21, 2017) • The choice of included study designs was justified • The review contained an explicit statement that the review methods were established prior to the conduct of the review • A flow chart of study selection was provided • A list of included studies was provided and the characteristics of included studies were described in detail • The quality of included studies was assessed using the Drummond checklist for economic evaluations and the from Philips checklist for model-based economic evaluations • Source of funding was disclosed as is unlikely to have influenced the findings of the review (funding support came through the a Swiss National Science Foundation grant) • The authors stated that they had no conflicts of interest related to this review	• Study selection was not performed in duplicate • A grey literature search was not completed • It is unclear if data extraction or quality assessment were done in duplicate • A list of excluded studies was not provided (although the reasons for exclusion were) • Studies were excluded if they were not published in the English language, no justification provided • There was no discussion on the possibility of publication bias • Review authors did not report on source of funding for the included studies • The two relevant primary studies were conducted in the US and the UK; findings may not be generalizable to the Canadian setting
Huoponen, 2015[19]	
• The objectives and inclusion/exclusion criteria were clearly stated and included components of population, intervention, comparator, and outcomes • Multiple databases were searched (Ovid Medline, Cochrane Library, and SCOPUS). In addition, a manual search of references from identified literature was performed • Grey literature searching was using other relevant websites and databases (Centre for Reviews and Dissemination, Current Controlled Trials, ClinicalTrials.gov, and PROSPERO) • Search terms and dates were provided (June 2014) • The choice of included study designs was justified • A flow chart of study selection was provided • A list of included studies was provided and the characteristics of included studies were described in detail • A list of excluded studies and their reasons for exclusion was provided • The quality of included studies was assessed using the	• It is unclear whether the review methods were established prior to conducting the review (no mention of a protocol) • Study selection, quality assessment, and data extraction were not performed in duplicate (all were conducted by a single author) • Studies were excluded if they were not published in the English language, no justification provided • There was no discussion on the possibility of publication bias • The two relevant primary studies were conducted in the US and the UK; findings may not be generalizable to the Canadian setting

Table 5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR II[15]

Strengths	Limitations
Drummond checklist and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines. The from Philips checklist was used for model-based economic evaluations • Review authors reported on source of funding for the included studies • The authors stated that they had no conflicts of interest and that no financial support had been received for this review	
Tang, 2013[20]	
• The objectives and inclusion/exclusion criteria were clearly stated and included components of population, intervention, comparator, and outcomes • Multiple databases were searched (PubMed, EMBASE, ABI/INFORM, Tuft's Cost-Effectiveness Analysis Registry Database, Cochrane National Health Service Economic Evaluation Database, International Pharmaceutical Abstracts, Web of Science, and Google Scholars). In addition, a manual search of references from identified literature was performed • Search terms and dates were provided (June 2011, updated June 2012) • Study selection and data extraction were completed in duplicate and described in detail • The choice of included study designs was justified • A flow chart of study selection was provided • A list of included studies was provided and the characteristics of included studies were described in detail • The quality of included studies was assessed in duplicate using the Drummond checklist • Review authors reported on source of funding for the included studies • The authors stated that they had no conflicts of interest related to this review • Sources of funding were disclosed and were unlikely to have influenced the findings of the review	• It is unclear whether the review methods were established prior to conducting the review (no mention of a protocol) • A grey literature search was not completed • A list of excluded studies was not provided (although the reasons for exclusion were) • Studies were excluded if they were not published in the English language, no justification provided • There was no discussion on the possibility of publication bias • The two relevant primary studies were conducted in the US and the UK; findings may not be generalizable to the Canadian setting

Table 6: Strengths and Limitations of Clinical Studies using the Downs and Black Checklist[16]

Strengths	Limitations
Wu, 2016[21]	
• The objectives, interventions, controls, and main outcomes are clearly described • Detailed methodology on patient recruitment and assessment of inclusion/exclusion criteria is included • Population characteristics were clearly described and were tested for statistically significant differences at baseline (there were no significant differences between treatment groups) • Compliance with the intervention was reliable • The major findings of the study were presented in tabular form and clearly described • Estimates of random variability were reported • Adverse events were recorded as part of the study • Length of follow-up was consistent between the treatment and control groups (14 weeks and 30 weeks after treatment initiation) • No patients were lost to follow-up in either treatment group • Study participants, care providers, and setting appear to be representative of the population and care setting of interest • Sources of funding were disclosed (the Wenzhou Municipal Science and Technology Commission Major Projects Funds) and were unlikely to have influenced the findings of the study • The authors declared that they had no conflicts of interest	• Although patients were randomized to treatment arms, details on the methodology used to randomize are lacking. "The cases were randomly divided into infliximab treatment group (N = 20) and conventional therapy group (N = 22) by the table of random number"[21] (*p*2) is the only information provided • Randomization concealment is unknown • The blinding of study participants and outcome assessors was not described in the study; therefore this is assumed to be an open-label trial • Actual probability values (*P*-values) were not reported • Single-centre study (conducted in China), may not be generalizable to other centres • No power calculation performed, low numbers in intervention groups, so unlikely to have had enough power to detect a statistically meaningful difference for several outcomes of interest

N = number of patients.

Table 7: Strengths and Limitations of Economic Studies using the Drummond Checklist[17]

Strengths	Limitations
Baji, 2018[22]	
Study design • The research questions, economic importance of the research question, viewpoints of the analysis, and rationale for choosing alternative interventions compared were clearly stated • The treatment strategies being compared were clearly described • The form of economic evaluation used was stated (7-state Markov model) • The choice of form of economic evaluation was justified in relation to the questions addressed **Data collection** • The sources of effectiveness estimates and drug costs were provided and described in detail • The primary outcome measures for the economic evaluation were clearly stated • Methods to value benefits were stated • Details of the subjects from whom valuations were obtained were given • Productivity loss was considered in the sensitivity analysis providing an assessment from the societal perspective • Details of currency were given (all costs were reported in 2015 euros, €) • The structure of the Markov model was clearly described **Analysis and interpretation of results** • Time horizon of costs and benefits was stated (5 years) • The discount rates were stated (rates ranged between 1.5% and 4% depending on the country) • The approach to sensitivity analysis was given • The choice of variables for sensitivity analysis were justified • The answer to the study question is given • Incremental analysis was reported • Conclusions follow from the data reported	• The choice of using a third-party payer viewpoint was not justified by the authors • Justification for selecting various discount rates was not provided • Conflicts of interest were stated by all study authors, including significant ties with industry • The study was funded by an unrestricted grant from Pfizer Hospira UK, a pharmaceutical company that offers several biologic therapies for the treatment of Crohn's disease • The findings of this European-based study may not be generalizable to other health systems

Appendix 4: Main Study Findings and Authors' Conclusions

Table 8: Summary of Findings Included Systematic Reviews and Meta-Analyses

<table>
<tr><th>Main Study Findings</th><th>Authors' Conclusion</th></tr>
<tr><td colspan="2">Pillai, 2017[18]</td></tr>
<tr><td>Systematic review that investigated the cost-effectiveness of various treatment strategies for IBD (particularly biological agents).

Relevant individual studies: The systematic review included 2 relevant economic evaluations on the cost-effectiveness of biologics compared with immunomodulators or antibiotics for fistulizing Crohn's disease.

Findings: The systematic review presented results on treatment costs, QALYs, and ICERs that could be extracted for the relevant studies.

Comparison of several treatment strategies for fistulizing CD with respect to several outcomes
<table>
<tr><th>Primary study citation</th><th>Treatment strategy</th><th>Inflated cost (2015 PPP)</th><th>QALY</th><th>ICER (PPP/QALY)</th></tr>
<tr><td rowspan="4">Arsenau, 2001[24]</td><td>6-MP and metronidazole</td><td>4,118.09</td><td>0.76</td><td>Reference</td></tr>
<tr><td>Initial infliximab induction infusions plus combination with 6-MP and metronidazole if treatment failure</td><td>14,234.03</td><td>0.78</td><td>505,796.84</td></tr>
<tr><td>Initial infliximab induction infusions with episodic reinfusion if treatment failure</td><td>14,389.13</td><td>0.78</td><td>513,552.06</td></tr>
<tr><td>6-MP and metronidazole followed by infliximab induction infusions with episodic reinfusion if treatment failure</td><td>9,482.71</td><td>0.77</td><td>536,461.97</td></tr>
<tr><td rowspan="2">Lindsay, 2008[25]</td><td>Standard care (immunomodulators and/or corticosteroids)</td><td>58,609.67</td><td>2.247</td><td>Reference</td></tr>
<tr><td>Infliximab initial infusions and maintenance therapy</td><td>69,773.24</td><td>2.449</td><td>55,265.19</td></tr>
</table>
ICER = incremental cost-effectiveness ratio; MP = mercaptopurine; PPP = purchasing power parity; QALY = quality-adjusted life year.
Note: All costs were adjusted to reflect 2015 purchasing power parity using OECD rates.
Table reproduced from: Pillai et al. PLoS One. 2017;12(10):e0185500.[18]</td><td>"The results of this review have major implications for future research in this field. Biologic agents were associated with ICERs above 100,000 PPP/QALY in the majority of studies for CD and UC; however, their use consistently demonstrated improvements in quality of life and remission rates. In the future, cost-effectiveness of biologic agents may improve as the market price falls and with the introduction of biosimilars. Future economic models need to strengthen existing literature by more accurately reflecting real world treatment pathways, ensuring the chronic and dynamic nature of IBD is captured and accounting for indirect, as well as direct costs, incurred by the health system and the patients."[18] (p17)

Note: The authors did not make any conclusions specific to fistulizing CD</td></tr>
<tr><td colspan="2">Huoponen, 2015[19]</td></tr>
<tr><td>Systematic review that sought to evaluate the existing evidence regarding the cost-effectiveness of biologics for the treatment of IBDs (CD and UC).

Relevant individual studies: The systematic review included 2 relevant economic evaluations on the cost-effectiveness of biologics compared with immunomodulators or antibiotics for fistulizing Crohn's disease.

Findings: The systematic review presented ICERs that could be extracted for the relevant studies.

Comparison of several treatment strategies for fistulizing CD with respect to several outcomes
<table>
<tr><th>Primary study citation</th><th>Treatment strategy</th><th>ICER (cost/QALY)</th></tr>
<tr><td rowspan="3">Arsenau, 2001[24]</td><td>6-MP and metronidazole</td><td>Reference</td></tr>
<tr><td>First-line infliximab</td><td>438,617</td></tr>
<tr><td>Infliximab episodic reinfusion</td><td>445,477</td></tr>
</table></td><td>"In conclusion, biologics seem to be cost-effective for the induction treatment of active and severe IBD, but not for the maintenance treatment. Whether there are differences in the cost-effectiveness between biologics remains unclear."[19] (p20)

Note: The authors did not make any conclusions specific to fistulizing CD</td></tr>
</table>

Table 8: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings			Authors' Conclusion
	Second-line infliximab episodic reinfusion	465,394	
Lindsay, 2008[25]	Standard care (immunomodulators and/or corticosteroids)	Reference	
	Infliximab	51,397	

ICER = incremental cost-effectiveness ratio; MP = mercaptopurine; QALY = quality-adjusted life year.
Note: All costs were adjusted to 2014 euro (€).
Table reproduced from: Huoponen and Blom. *PLoS One.* 2015;10(12):e0145087.[19]

Tang, 2013[20]

Systematic review that summarized the current literature on economic studies that evaluated biological agents, specifically, infliximab, adalimumab, certolizumab pegol, and natalizumab, when used in the treatment of moderate-to-severe CD.

Relevant individual studies: The systematic review included 2 relevant economic evaluations on the cost-effectiveness of biologics compared with immunomodulators or antibiotics for fistulizing Crohn's disease.

Findings: The systematic review presented ICERs that could be extracted for the relevant studies.

Comparison of several treatment strategies for fistulizing CD with respect to several outcomes

Primary study citation	Treatment strategy	ICER (cost/QALY)
Arsenau, 2001[24]	6-MP and metronidazole	Reference
	Intervention 1: Infliximab (5 mg/kg at weeks 0, 2, and 6; nonresponsive patients crossed over to 6-MP and metronidazole.	355,450[a]
	Intervention 2: Infliximab (5 mg/kg) at weeks 0, 2, and 6; nonresponsive patients crossed over to episodic reinfusion	360,900[a]
	Intervention 3: 6-MP and metronidazole; nonresponsive patients crossed over to intervention 2	377,000[a]
Lindsay, 2008[25]	Standard care (immunomodulators and/or corticosteroids)	Reference
	infliximab (5 mg/kg) at weeks 0, 2, 6, and every 8 weeks thereafter	29,752[b]

ICER = incremental cost-effectiveness ratio; MP = mercaptopurine; QALY = quality-adjusted life year.
[a]The ICER results were denoted in 1999 United States dollars ($).
[b]The ICER results were denoted in 2005/2006 British pounds (£).

"Biological therapies used in CD management are cost-effective in specific clinical scenarios. The cost-effectiveness of each biologic therapy for CD may be optimized by (1) identifying the optimal time frame in which biological and standard therapies are each administered over a fixed period, (2) exploring the scenarios in which patients switch to standard therapy or other biologics after failing a given biological therapy, and (3) investigating other population-based factors contributing to the variations in treatment cost-effectiveness. Given the limited number of published studies, the diversity of model assumptions and data sources, and the relatively short period of market time for biologics, identifying patient subgroups in which biological therapies are most cost-effective remains an important gap in the literature."[20] (*p*2692-2693)

Note: The authors did not make any conclusions specific to fistulizing CD

CD = Crohn's disease; IBD = inflammatory bowel disease; ICER = incremental cost-effectiveness ratio; PPP = purchasing power parity; QALY = quality-adjusted life year; UC = ulcerative colitis.

Table 9: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Wu, 2016[21]	
RCT that investigated the potential application of enteral nutrition in CD patients with intestinal fistulas undergoing infliximab treatment or conventional therapy (methylprednisolone and azathioprine). Comparison of infliximab treatment (IFX) and conventional therapy (CT) with respect to several outcomes	"IFX in combination with [enteral nutrition] induces and promotes remission in patients with CD complicated by fistula, with a better prospect of achieving a curative effect in the future. This treatment can also reduce inflammation of patients with CD, improve the nutritional status, and promote the healing of the fistula. It is worthy of clinical treatment."[21] (*p*5)

Outcome measure	Mean value (SD) Treatment group IFX (N = 20)	Mean value (SD) Treatment group CT (N = 22)	Between group significance[a] (*P*-value)
Various laboratory indicators			
ESR (mm/h)			
Pre-treatment	36.43 (3.21)	31.78 (3.03)	NR
Follow-up (14 weeks)	25.29 (2.92)	26.08 (2.89)	NR
Follow-up (30 weeks)	13.21 (1.86)	14.24 (1.92)	NS
CRP (mg/L)			
Pre-treatment	31.12 (6.99)	30.97 (6.86)	NR
Follow-up (14 weeks)	12.35 (4.23)	10.87 (4.16)	NR
Follow-up (30 weeks)	5.23 (2.63)	5.78 (2.59)	NS
BMI (kg/m^2)			
Pre-treatment	17.52 (1.89)	17.66 (1.98)	NR
Follow-up (14 weeks)	19.19 (2.13)	18.21 (2.09)	NR
Follow-up (30 weeks)	20.26 (2.65)	19.98 (2.49)	NS
ALB (g/L)			
Pre-treatment	32.58 (1.67)	33.12 (1.61)	NR
Follow-up (14 weeks)	38.92 (2.35)	37.88 (2.29)	NR
Follow-up (30 weeks)	39.89 (2.72)	38.81 (2.69)	NS
Clinical outcomes			
CDAI score			
Pre-treatment	325.6 (70.8)	309.9 (69.3)	NR
Follow-up (14 weeks)	235.5 ± 62.8	246.8 (63.9)	NR
Follow-up (30 weeks)	125.6 ± 42.5	178.6 (46.6)	<0.05
SES-CD score			
Pre-treatment	8.6 (2.2)	8.1 (2.0)	NR
Follow-up (14 weeks)	3.5 (0.8)	6.2 (1.2)	NR
Follow-up (30 weeks)	1.6 (0.5)	4.9 (0.8)	<0.05
Fistula healing (% of total)			
Pre-treatment	0%	0%	NR
Follow-up (14 weeks)	40.0%	13.6%	NR
Follow-up (30 weeks)	90.0%	27.3%	<0.05

[a]The threshold for statistical significance was set to P < 0.05.
ALB = albumin; BMI = body mass index; CDAI = Crohn's disease activity index; CRP = C-reactive protein; CT = conventional therapy; ESR = erythrocyte sedimentation rate; IFX = infliximab treatment; N = number of patients; NS = non-significant; SD = standard deviation; SES-CD = Crohn's disease simplified endoscopic score.

Adverse events: A decrease in the number of white blood cells (<4×10^9/L) was observed in 15% and 22.7% of patients undergoing infliximab treatment or conventional therapy, respectively. Two patients in the infliximab group had diarrhea and infusion, who reported dizziness, chest tightness, cold sweat, and rashes on the body. No other adverse effects were reported. The statistical significance of these findings was not reported.

CD = Crohn's disease; IFX = infliximab.

Table 10: Summary of Findings of Included Economic Evaluation

Main Study Findings	Authors' Conclusion
Baji, 2018[22]	
Economic evaluation that examined the cost-effectiveness of the different treatment sequences with available biologicals (infliximab, biosimilar-infliximab, adalimumab, vedolizumab) compared to standard care (sulfasalazine and prednisolone) for the treatment of fistulizing CD in nine European countries (Belgium, France, Germany, Hungary, Italy, Spain, Sweden, the Netherlands, and the UK) using a Markov model-based cost-effectiveness analysis. Summary of relevant findings: - The model inputs for standard care by country used in both the list price and real price analyses ○ **Standard care** ▪ QALY • Belgium = 2.0973; France = 2.027; Germany = 2.031; Hungary = 1.990; Italy = 2.033; Netherlands = 2.100; Spain = 2.031; Sweden = 2.034; UK = 2.007 ▪ Cost (shown in €) • Belgium = 12,250; France = 11,786, Germany = 15,956; Hungary = 3,595; Italy = 15,047; Netherlands = 13,717; Spain = 18,272; Sweden = 33,178; UK = 20,273 - The cost-effectiveness of one biological versus standard care by country (using list prices) ○ **Biosimilar-infliximab vs. standard care** ▪ Δ QALY to standard care • Belgium = 0.2524; France = 0.2462; Germany = 0.2461; Hungary = 0.2436; Italy = 0.2460; Netherlands = 0.2523; Spain = 0.2461; Sweden = 0.2460; UK =0.2442 ▪ Δ cost to standard care (shown in €) • Belgium = 9,697; France = 10,764; Germany = 17,854; Hungary = 8,450; Italy = 10,840; Netherlands = 14,910; Spain = 13,394; Sweden = 17,095; UK = 15,603 ▪ ICER to standard care (cost/QALY) • Belgium = 38,420; France = 43,721; Germany = 72,551; Hungary = 34,684; Italy = 44,059; Netherlands = 59,101; Spain = 54,427; Sweden = 69,491; UK = 63,908 ○ **Infliximab vs. standard care** ▪ Δ QALY to standard care • Belgium = 0.252; France = 0.246; Germany = 0.246; Hungary = 0.244; Italy = 0.246; Netherlands = 0.252; Spain = 0.246; Sweden = 0.246; UK = 0.244 ▪ Δ cost to standard care (shown in €) • Belgium = 9,697; France = 10,764; Germany = 23,512; Hungary = 12,007; Italy = 14,322; Netherlands = 14,910; Spain = 15,971; Sweden = 19,597; UK = 17,040 ▪ ICER to standard care (cost/QALY) • Belgium = 38,420; France = 43,721; Germany = 95,540; Hungary = 49,286; Italy = 58,215; Netherlands = 59,101; Spain = 64,898; Sweden = 79,663; UK = 69,793 ○ **Adalimumab vs. standard care** ▪ Δ QALY to standard care • Belgium = 0.136; France = 0.132; Germany = 0.132; Hungary = 0.131; Italy = 0.132; Netherlands = 0.136; Spain = 0.132; Sweden = 0.132; UK = 0.131 ▪ Δ cost to standard care (shown in €) • Belgium = 9,091; France = 8,151; Germany = 17,480; Hungary = 7,941; Italy = 10,361; Netherlands = 11,411; Spain = 11,417; Sweden = 14,157; UK = 9,989 ▪ ICER to standard care (cost/QALY) • Belgium = 66,921; France = 61,562; Germany = 132,071; Hungary = 60,646; Italy = 78,296; Netherlands = 84,031; Spain = 86,263; Sweden = 106,990; UK = 76,099 ○ **Vedolizumab vs. standard care** ▪ Δ QALY to standard care	"In clinical practice, treatment sequences of biologicals are applied for active fistulising CD, however underlying health economic analyses are lacking. The suggested first-choice biological treatment is bsIFX. In case of treatment failure, switching to ADA then to VEDO provides meaningful additional health gains but at increased costs."[22] (*p*320)

Table 10: Summary of Findings of Included Economic Evaluation

Main Study Findings	Authors' Conclusion
• Belgium = 0.168; France = 0.164; Germany = 0.164; Hungary = 0.162; Italy = 0.164; Netherlands = 0.168; Spain = 0.164; Sweden = 0.164; UK = 0.162 ▪ Δ cost to standard care (shown in €) • Belgium = 14,117; France = 17,799; Germany = 18,964; Hungary = 17,504; Italy = 14,307; Netherlands = 14,598; Spain = 23,295; Sweden = 20,228; UK = 20,163 ▪ ICER to standard care (cost/QALY) • Belgium = 83,806; France = 108,561; Germany = 115,696; Hungary = 108,026; Italy = 87,299; Netherlands = 86,688; Spain = 142,118; Sweden = 123,437; UK = 124,090 - The cost-effectiveness of one biological versus standard care by country (using real prices). Note: QALY gains are equal to those from the list price analysis as only drug prices were modified. Vedolizumab vs. standard care was not presented again as the list price was assumed to be the same as the real price. ○ **Biosimilar-infliximab vs. standard care** ▪ Δ cost to standard care (shown in €) • Belgium = 6,850; France = 7,584; Germany = 12,716; Hungary = 5,936; Italy = 7,705; Netherlands = 10,737; Spain = 9,658; Sweden = 13,797; UK = 11,724 ▪ ICER to standard care (cost/QALY) • Belgium = 27,141; France = 30,807, Germany = 51,670; Hungary = 24,364; Italy = 31,319; Netherlands = 42,558; Spain = 39,245; Sweden = 56,086; UK = 48,017 ○ **Infliximab vs. standard care** ▪ Δ cost to standard care (shown in €) • Belgium = 6,850; France = 7,584; Germany = 16,676; Hungary = 8,426; Italy = 10,143; Netherlands = 10,737; Spain = 11,462; Sweden = 15,549; UK = 12,729 ▪ ICER to standard care (cost/QALY) • Belgium = 27,141; France = 30,807; Germany = 67,762; Hungary = 34,585; Italy = 41,228; Netherlands = 42,558; Spain = 46,575; Sweden = 63,206; UK = 52,137 ○ **Adalimumab vs. standard care** ▪ Δ cost to standard care (shown in €) • Belgium = 7,398; France = 6,621; Germany = 14,196; Hungary = 6,378; Italy = 8,457; Netherlands = 9,383; Spain = 9,409; Sweden = 12,220; UK = 8,228 ▪ ICER to standard care (cost/QALY) • Belgium = 54,459; France = 50,005; Germany = 107,255; Hungary = 48,713; Italy = 63,912; Netherlands = 69,100; Spain = 71,091; Sweden = 92,354; UK = 62,683 - One-way sensitivity analyses were performed for biosimilar-infliximab versus standard care for several parameters ○ **Base case ICER results** ▪ Belgium = 38,420; France = 43,721; Germany = 72,551; Hungary = 34,684; Italy = 44,059; Netherlands = 59,101; Spain = 54,427; Sweden = 69,491; UK = 63,908 ○ **Body weight (base case estimate was 65 kg)** ▪ 60 kg • Belgium = -8%; France = -8%; Germany = -7%; Hungary = -8%; Italy = -7%; Netherlands = -7%; Spain = -7%; Sweden = -5%; UK = -6% ▪ 70 kg • Belgium = 8%; France = 8%; Germany = 7%; Hungary = 8%; Italy = 7%; Netherlands = 7%; Spain = 7%; Sweden = 5%; UK = 6% ○ **Time horizon (base case estimate was 5 years)** ▪ 10 years • Belgium = -6%; France = -5%; Germany = -5%; Hungary = -6%; Italy = -5%; Netherlands = -6%; Spain = -5%; Sweden = -5%; UK = -5%	

Table 10: Summary of Findings of Included Economic Evaluation

Main Study Findings	Authors' Conclusion
○ **Surgery and inpatient cost** ▪ <u>+10%</u> • Belgium = -0.2%; France = -0.2%; Germany = -0.2%; Hungary = -0.2%; Italy = -0.3%; Netherlands = -0.2%; Spain = -0.1%; Sweden = -0.2%; UK = -0.2% ▪ <u>-10%</u> • Belgium = 0.2%; France = 0.2%; Germany = 0.2%; Hungary = 0.2%; Italy = 0.3%; Netherlands = 0.2%; Spain = 0.1%; Sweden = 0.2%; UK = 0.2% ○ **Discounting (base case used country specific discounting)** ▪ <u>No discounting</u> • Belgium = -2%; France = -4%; Germany = -4%; Hungary = -4%; Italy = -4%; Netherlands = -1%; Spain = -4%; Sweden = -5%; UK = -5% ○ **Productivity loss (base case did not calculate productivity loss)** ▪ <u>Productivity loss included</u> • Belgium = -27%; France = -22%; Germany = -12%; Hungary = -6%; Italy = -18%; Netherlands = -15%; Spain = -11%; Sweden = -15%; UK = -10% ○ **Utility values (base case used values from Lindsay et al., 2008)** ▪ <u>+10%</u> • Belgium = -9%; France = -9%; Germany = -9%; Hungary = -9%; Italy = -9%; Netherlands = -9%; Spain = -9%; Sweden = -9%; UK = -9% ▪ <u>-10%</u> • Belgium = 11%; France = 11%; Germany = 11%; Hungary = 11%; Italy = 11%; Netherlands = 11%; Spain = 11%; Sweden = 11%; UK = 11% ○ **Medicine wasting (base case used no wasting)** ▪ <u>Wasting</u> • Belgium = 15%; France = 15%; Germany = 15%; Hungary = 15%; Italy = 15%; Netherlands = 14%; Spain = 14%; Sweden = 10%; UK = 13% ○ **Age of patients (base case used 40 years)** ▪ <u>35 years</u> • Belgium = 0.1%; France = 0.1%; Germany = 0.1%; Hungary = 0.3%; Italy = 0.1%; Netherlands = 0.1%; Spain = 0.1%; Sweden = 0.1%; UK = 0.1% ▪ <u>45 years</u> • Belgium = -0.2%; France = -0.2%; Germany = -0.2%; Hungary = -0.5%; Italy = -0.1%; Netherlands = -0.2%; Spain = -0.2%; Sweden = -0.1%; UK = -0.1%	

<u>Δ = difference in;</u> ADA = adalimumab; bsIFX = biosimilar-infliximab; ICER = incremental cost- effectiveness ratio; QALY = quality-adjusted life year; VEDO = vedolizumab.

Appendix 5: Overlap between Included Systematic Reviews

Table 11: Relevant Primary Study Overlap between Included Systematic Reviews

Primary Study Citation	Systematic Review Citation		
	Pillai, 2017[18]	Huoponen, 2015[19]	Tang, 2013[20]
Arseneau, 2001[24]	X	X	X
Lindsay, 2008[25]	X	X	X

X = the primary study was included in the systematic review and relevant data was extracted for our review.
Note: All three systematic reviews were included in this review despite having complete relevant study overlap. The reason for this is that each systematic review used distinct search strategies, inclusion and exclusion criteria, methods of adjusting currency for inflation, quality appraisal tools, and presented data from the relevant primary studies in various levels of detail.

Appendix 6: Additional References of Potential Interest

Previous CADTH Reports

Anti-TNF-α drugs for refractory inflammatory bowel disease: clinical- and cost-effectiveness analyses. (CADTH Technology report no. 120). Ottawa (ON): CADTH; 2009: https://www.cadth.ca/sites/default/files/pdf/H0479_Anti_TNF_a_Drugs_for_Refractory_Inflammatory_Bowel_Disease_tr_e.pdf. Accessed 2019 Feb 25.

Systematic Reviews and Meta-Analyses

Study Protocols

Stanic Benic M, Giljaca V, Vlahovic-Palcevski V. The impact of biological interventions on health-related quality of life in adults with Crohn's disease. *Cochrane Database Syst Rev*. 2018 (11). https://www.cochrane.org/CD012973/IBD_impact-biological-interventions-health-related-quality-life-adults-crohns-disease. Accessed 2019 Feb 25.

Randomized Controlled Trials

Alternative Population – Not Specific to Patients with Fistulizing Crohn's Disease

Cozijnsen MA, van Pieterson M, Samsom JN, Escher JC, de Ridder L. Top-down infliximab study in kids with Crohn's disease (TISKids): an international multicentre randomised controlled trial. *BMJ Open Gastroenterol*. 2016;3(1):e000123.
PubMed: PM28090335

Colombel JF, Reinisch W, Mantzaris GJ, et al. Randomised clinical trial: deep remission in biologic and immunomodulator naive patients with Crohn's disease - a SONIC post hoc analysis. *Aliment Pharmacol Ther*. 2015 Apr;41(8):734-746.
PubMed: PM25728587

Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med*. 2010 Apr 15;362(15):1383-1395.
PubMed: PM20393175

Non-Randomized Studies

Alternative Population – Not Specific to Patients with Fistulizing Crohn's Disease

Hoekman DR, Stibbe JA, Baert FJ, et al. Long-term outcome of early combined immunosuppression versus conventional management in newly diagnosed Crohn's disease. *J Crohns Colitis*. 2018 Apr 27;12(5):517-524.
PubMed: PM29401297

Diamanti A, Basso MS, Gambarara M, et al. Positive impact of blocking tumor necrosis factor alpha on the nutritional status in pediatric Crohn's disease patients. *Int J Colorectal Dis*. 2009 Jan;24(1):19-25.
PubMed: PM18797887

Economic Evaluations

Alternative Population – Not Specific to Patients with Fistulizing Crohn's Disease

Blackhouse G, Assasi N, Xie F, et al. Canadian cost-utility analysis of initiation and maintenance treatment with anti-TNF-alpha drugs for refractory Crohn's disease. *J Crohns Colitis*. 2012 Feb;6(1):77-85.
PubMed: PM22261531

Loftus EV, Jr., Johnson SJ, Wang ST, Wu E, Mulani PM, Chao J. Risk-benefit analysis of adalimumab versus traditional non-biologic therapies for patients with Crohn's disease. *Inflamm Bowel Dis*. 2011 Jan;17(1):127-140.
PubMed: PM20848523

Ananthakrishnan AN, Hur C, Juillerat P, Korzenik JR. Strategies for the prevention of postoperative recurrence in Crohn's disease: results of a decision analysis. *Am J Gastroenterol*. 2011 Nov;106(11):2009-2017.
PubMed: PM21788991

Bodger K, Kikuchi T, Hughes D. Cost-effectiveness of biological therapy for Crohn's disease: Markov cohort analyses incorporating United Kingdom patient-level cost data. *Aliment Pharmacol Ther*. 2009 Aug;30(3):265-274.
PubMed: PM19438428

Loftus EV, Jr., Johnson SJ, Yu AP, Wu EQ, Chao J, Mulani PM. Cost-effectiveness of adalimumab for the maintenance of remission in patients with Crohn's disease. *Eur J Gastroenterol Hepatol*. 2009 Nov;21(11):1302-1309.
PubMed: PM19465858