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Inflammatory Bowel Disease-Attributable Costs and Cost-effective Strategies in the United States: A Review

K.T. Park, MD, and Dorsey Bass, MD

Abstract: The United States spends more for healthcare than any other country in the world. With the rising prevalence of both Crohn's disease and ulcerative colitis, inflammatory bowel disease (IBD) represents the leading chronic gastrointestinal disease with increasing healthcare expenditures in the US. IBD costs have shifted from inpatient to outpatient care since the introduction of biologic therapies as the standard of care. Gastroenterologists need to be aware of the national cost burden of IBD and clinical practices that optimize cost-efficiency. This investigation offers a systematic review of the economics of IBD and evidence-based strategies for cost-effective management.

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Key Words: healthcare cost, inflammatory bowel disease, cost effectiveness analysis

Inflammatory bowel disease (IBD) is a chronic disorder with a usual relapsing and remitting course. A recent epidemiological investigation estimates that nearly 4 million persons worldwide are affected with either ulcerative colitis (UC) or Crohn's disease (CD), and ≈1.4 million of these cases occur in the United States.[1] In US children the prevalences of CD and UC are 43 and 28 per 100,000, respectively, and in US adults the prevalences of CD and UC are 201 and 238 per 100,000, respectively.[2] The incidence of IBD in minorities, especially among Asian Americans, seems to be increasing over the last two decades.[3] An observational case-controlled study by Longobardi et al[4] reported that patients with less than 5 years IBD diagnosis compared to non-IBD controls have increased emergency room visits (odds ratio [OR] = 2.41; 95% confidence interval [CI] = 1.49–3.88) and hospitalizations and surgical interventions (OR = 2.34; 95% CI = 1.09–4.19). IBD, therefore, represents a disease with an important economic impact on the healthcare system and the economy as a whole.

The main objective of this review is to provide a critical summary of recent literature on the topic of optimal management strategies and associated direct costs of IBD in the US. Although this article will focus mainly on investigations undertaken in the US, some studies from other countries are discussed for comparison purposes.

A MEDLINE search was conducted using the terms ulcerative colitis, Crohn's disease, inflammatory bowel disease, infliximab, healthcare cost, cost-effectiveness, cost-benefit, and cost-utility to find pertinent research articles published after 1995. Letters, editorials, and commentaries were excluded from the analysis, but a few references were included for discussion purposes. Approximately 600 original articles were reviewed for this summary, which discusses hospitalization costs, diagnostic tests, mesalamine and sulfasalazine, immunomodulators, biologics, surgical treatment, cost of nonadherence, and cost of opportunity loss.

OVERVIEW

Healthcare costs in the US are higher than any other country. Yu et al[5] showed in a recent systematic review that the cost of CD is more expensive in the US than in other Western countries. For patients with CD living in the US, direct medical costs were estimated to be $18,022–18,932 per patient per year compared to approximately $4,000–10,000 (converted from euros to dollars). Gibson et al[6] analyzed MarketScan databases from 1999–2005 to measure the cost burden of CD and UC. Commercially insured CD and UC patients in the US had annual medical expenditures of $18,963 and $15,020, respectively—significantly more than the $5,000 estimated for the patients in the matched comparison group of similar patients living outside the US. It is not known whether these increased expenditures result in better outcomes.

Kappelman et al[7] measured the direct costs of IBD in children and adults during 2003 and 2004 by analyzing insurance claims from 87 different health plans in 33 states. The estimated mean annual cost was $8,265 for CD and $5,066 for UC. The discrepancy between this study and the

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previous two studies is perhaps due to the reporting of actual reimbursements instead of charges to the insurer. This study also revealed that costs for patients under 20 years of age were higher than those for adults over 20 years of age, suggesting that focusing on effective management of IBD in pediatric patients could yield significant cost-efficient benefits. Also, more than one-third of the total IBD-related costs were attributable to inpatient management of disease, suggesting that reducing hospitalization through optimal maintenance of remission would decrease the overall cost-burden. A more recent study in 2010 by Kappelman et al[8] confirmed that healthcare utilization was disproportionately increased in younger IBD patients.

COST OF HOSPITALIZATION

Effective maintenance of IBD remission is directly linked to lower rates of hospitalization. Evidence points to inpatient costs as an important factor in increasing total costs of IBD. A multinational European and Israeli study showed that the majority of IBD-related healthcare expenditures were to inpatient medical and surgical management.[9] A Canadian study showed that medical inpatient costs for CD and UC were similar, but surgical costs were more for UC than for CD.[10] In an American study by Hillson et al,[11] a retrospective cost-analysis of medical claims showed that patients with severe UC, as compared to patients with mild or moderate UC, had more than twice the total cost burden ($26,875 versus $12,154 and $12,731, $P < 0.005$) and more than quadruple the inpatient cost burden ($13,516 versus $3235 and $2244). A retrospective analysis by Bickston et al[12] of three age groups (<18 years, 18–64 years, >64 years) using the PharMetrics database compared UC patients to an IBD-free group that was matched for age and gender. This study showed that the mean annual inpatient costs for a UC patient were $5,771 versus $966 for a non-UC patient ($P < 0.001$). Of the three age groups, pediatric-adolescent patients with UC (<18 years) had the highest mean annual all-cause total healthcare costs at $23,113. Adults incurred less costs, ranging from $12,693 to $15,811 per year.

The cost of hospitalization for CD was characterized by Cohen et al[13] using a US single-center database review of hospitalized CD patients. The average total cost of hospitalization was $35,378 with mean surgical and medical hospitalization charges of $46,353 and $20,744, respectively. Mean surgical and medical hospital reimbursements were $28,946 and $12,666, respectively. Silverstein et al[14] created a Markov model that showed that the larger proportion of total charges in CD was attributable to surgical care. These two studies, reported over a decade ago, did not take into consideration the impact of biologics on the medical options for CD.

Cohen et al[15] more recently analyzed the effects of fistulizing disease on CD costs using the PharMetrics database. Among the total 13,454 CD patients identified over a 5-year span, 771 (5.7%) patients had fistula formation in the year following diagnosis. The total median cost per patient was greater than $4,000 more for the patients who developed fistulas ($10,868 versus $6,268). The cost differential was mainly due to hospitalization and surgery.

DIAGNOSTIC TESTS

The cost-effectiveness of many diagnostic and screening tests for IBD is unknown, e.g., magnetic resonance enterography (MRE). Levesque et al[16] modeled the comparison of computed tomographic enterography (CTE) versus small-bowel follow-through (SBFT) for patients with moderate to high pretest probability of small bowel CD. Of note, the lifetime radiation risk with CTE and SBFT was not modeled in this analysis. The resulting incremental cost-effectiveness ratio (ICER) was less than $54,000 per quality-adjusted life-years (QALYs) gained when CTE was chosen over SBFT. The addition of wireless capsule endoscopy (WCE) after an ileocolonoscopy and negative SBFT or CTE resulted in an ICER >$500,000 per QALY. The use of MRE in evaluating the small bowel in CD is more expensive but eliminates the risk of ionizing radiation from CTE and SBFT. Future standard of practice for diagnostic evaluation of CD may depend on the relative diagnostic accuracy, safety, and cost-effectiveness of MRE. WCE has been proposed as a cost-effective modality when used as a single diagnostic test. Goldfarb et al[17] used a decision tree model to show cost-savings of $291 from the payer's perspective in choosing WCE over SBFT and colonoscopy in the initial workup of CD. Although WCE is less invasive and does not have a potentially serious anesthesia risk, WCE cannot provide tissue diagnosis via biopsy, which is often necessary for a definitive diagnosis of IBD. Using WCE as a sole diagnostic test may also increase risk of capsule retention and subsequent surgery.

The cost-effectiveness of various intervals of colonoscopic screening for colorectal cancer (CRC) in chronic UC (with or without 5-aminosalicylates [5-ASA] chemoprevention for dysplasia) has been investigated, although without a clear consensus.[18,19] Rubenstein et al[20] reported that the ideal colonoscopic screening interval for CRC in UC patients treated with 5-ASA is every 3 years. This every-3-year strategy resulted in an ICER of $63,387 per QALY, which is less than the assumed willingness-to-pay threshold of $100,000 per QALY. In comparison, an annual colonoscopic surveillance strategy would cost nearly $1 million per QALY. For a patient not receiving 5-ASA therapy, the model revealed that annual surveillance was the ideal strategy, costing $69,100 per QALY.

Diagnostic approaches to pouchitis, a potentially chronic condition with significant impact on quality of life

to UC patients after subtotal colectomy and ileal pouch–anal anastomosis (IPAA), have been evaluated. Commonly used clinical strategies include either treatment with antibiotics based on symptomatology alone or pouch endoscopy with or without biopsies prior to antibiotic treatment. Shen et al[21] analyzed a decision tree with six competing strategies. Although an empiric trial of metronidazole had the lowest cost among the six strategies, pouch endoscopy without biopsies had only an additional $50 cost. Pouch endoscopy without biopsy was the preferred strategy, based on more timely diagnosis and avoidance of unnecessary antibiotic therapy, as well as cost benefits. Parsi et al[22] reported that obtaining fecal lactoferrin prior to diagnosing pouchitis may be a cost-effective strategy, resulting in a 31% reduction in antibiotic use with a marginal decrease in effectiveness.

5-ASA COMPOUNDS

IBD treatment with 5-ASA compounds, used primarily for mild to moderate colonic and rectal disease, is generally more affordable than immunomodulator or biologic therapies. According to a popular online pharmacy,[23] for an average adult, enteric-coated sulfasalazine (500 mg four times daily) costs $50 per month and mesalamine (2.4 g/day) costs approximately $300 per month. Lialda costs approximately $700/month. Because these medications are prescribed for very long-term use, clinicians should take the cost differential into consideration when treating UC patients with mild to moderate disease.

Sulfasalazine is generally as effective as and more affordable than other ASA compounds. Nikfar et al[24] performed a meta-analysis on 20 randomized, placebo-controlled clinical trials comparing the efficacy and tolerability of sulfasalazine with mesalamine. They found that sulfasalazine did not significantly increase the relative risk (RR) for any adverse events compared to mesalamine (RR 0.76, 95% CI 0.54–1.07, $P = 0.11$). The investigators also reported a nonsignificant RR of 1.04 (95% CI of 0.89–1.21, $P = 0.63$) for overall improvement, indicating similar efficacy for sulfasalazine and mesalamine.

Mackowiak et al[25] demonstrated through a decision analysis that oral mesalamine failure led to an average cost of $11,500 per patient during the first 6 months after therapy. Comparing various 5-ASA compounds, balsalazide capsules produced 16% lower total costs and 32% improved outcomes (days without symptoms or steroids).

A study from the United Kingdom by Buckland and Bodger[26] performed a cost-utility analysis of the standard dose of mesalamine (2.4 g/day) versus high-dose mesalamine (4.8 g/day) in UC patients with moderately active disease. After a 12-week trial, results suggested that high-dose mesalamine was cost-effective, increasing QALYs by 0.0016.

5-ASA use in CD, on the other hand, has been shown repeatedly to be ineffective in maintaining CD remission, as confirmed in a recent Cochrane review by Akobeng and Gardener.[27] A cost-saving practice is to discontinue 5-ASA use as a maintenance drug for CD.

IMMUNOMODULATORS

There is no recent analysis evaluating the direct cost-effectiveness or utility of azathioprine (AZA), methotrexate, or 6-mercaptopurine (6MP).

Patients treated with immunomodulators need close monitoring of serious immunosuppressive and/or hepatotoxic side effects. Thiopurine methyltransferase (TPMT) screening prior to starting immunomodulators is important to prevent potentially life-threatening adverse reactions and is current practice in many clinical settings. Thiopurine metabolite monitoring may also enhance effective use of these agents, but has yet to be established as standard of care.

Recently, Dubinsky et al[28] performed a decision analysis showing the cost-effectiveness of TPMT screening and thiopurine metabolite monitoring to more quickly reach therapeutic levels of erythrocyte 6-thioguanine nucleotide and to maintain longer steroid-free response (>2 months). After a 1-year time horizon, the most expensive strategy ($7,142) was no TPMT screening or thiopurine metabolite monitoring, while the least costly alternative ($3,861) was TPMT screening alone.

An alternative to metabolite monitoring may be the monitoring of red blood cell mean corpuscular volume (MCV) and white blood cell count (WBC), since macrocytosis is a side effect of immunomodulator therapy. A recent retrospective study by Waljee et al[29] used machine learning to predict immunologic response in patients on immunomodulators. The investigators found that an MCV/WBC ratio of 12 or greater correlates to a 0.67 probability of clinical response to immunomodulators, whereas thiopurine metabolite levels predicted a 0.62 probability of clinical response. As the current manufacturer list price for thiopurine metabolite levels is $270 per panel versus $40 for complete blood count with differential, using MCV/WBC ratios to monitor clinical response to immunomodulator therapy is a potentially cost-saving practice.

BIOLOGICS

Biologics, e.g., infliximab and adalimumab, are monoclonal antibodies that bind tumor necrosis factor alpha (TNF-α). These treatments are the most expensive medical therapies available for IBD. For an adult, average wholesale price of infliximab typically ranges from $2,000 to $4,000 per infusion ($800 for 100 mg vial),[30] depending on the patient's weight. The average wholesale price of adalimumab is $2,000 per month ($1,000 for 40 mg vial),

depending on maintenance dosing frequency. Ollendorf and Lidsky[31] evaluated insurance claims from PharmMetrics for infliximab from 2000 to 2003 and reported that the mean hospital charges and paid amounts per infusion were $4,441 and $2,793, respectively. The average administration cost to a commercial insurer was $2,800.

Evidence points to clear efficacy of infliximab in IBD,[32,33] although its cost-effectiveness has yet to be conclusively proven in the US. The cost of infliximab to society has been investigated and discussed by experts from different countries.[34–37] One single-center cost-analysis from Spain by Saro et al[38] compared resource utilization before and after initiation of infliximab in CD patients. Although the cost for hospitalization was reduced from 62.4% to 6.4% of total costs, the overall cost of CD management more than doubled. Two recent studies from the United Kingdom evaluated the cost-effectiveness of infliximab therapy in CD and UC. Lindsay et al[39] analyzed a Markov model of hypothetical 60 kg adult CD patients treated with infliximab (5 mg/kg) every 8 weeks. Infliximab was cost-effective for both active luminal and fistulizing disease. Sensitivity analysis revealed patient body weight as an important factor in affecting cost-effectiveness. Tsai et al[40] analyzed a Markov model of hypothetical 73 kg adult UC patients over a 10 year horizon receiving infliximab (5 mg/kg) every 8 weeks for maintenance of remission. Infliximab was cost-effective for adult patients with moderate to severe UC. Sensitivity analysis revealed body weight and time horizon to be important factors affecting cost-effectiveness.

An American study by Arseneau et al[41] reported the incremental benefit of infliximab using a Markov model for treating CD perianal fistulae over a 1-year period. Compared to the base case scenario of 6MP and metronidazole, the three other alternative strategies using various infliximab frequencies yielded only minimal increase in effectiveness with an incremental cost-utility range of $355,450 to $377,000 per QALY. Sensitivity analysis showed that decreasing the infliximab cost to $304 per infusion reduced the cost-utility to $54,050 per QALY. Also in the US, a pediatric retrospective chart review by Condino et al[42] raises the possibility of reducing infliximab administration costs through a home infusion program. Among the 10 patients who received 59 home infusions with a dose range of 7.5–10 mg/kg, cost savings amounted to $1,335 per 100 mg infliximab. No serious adverse reactions were reported, and patient satisfaction was 9 out of 10 (10 = most satisfied).

Adalimumab is efficacious in CD, and with its subcutaneous route of delivery there is no need for monitored intravenous administration and its associated costs.[43] Recent studies have compared the cost and utility associated with adalimumab versus infliximab. One retrospective analysis raised the question of the cost-effectiveness of infliximab over the long-term since the majority (77%) of CD patients lost response after a 2-year period.[44] However, a more recent prospective investigation of 614 patients with CD and a median follow-up of 55 months reported sustained response of infliximab in 63.4% of the cohort.[45] It is not entirely known how quickly patients lose response on adalimumab therapy, although it is generally thought that a more sustained response is possible since adalimumab is not a chimeric antibody like infliximab and thus touted to be less antigenic.

Kaplan et al[46] determined that, in CD patients who no longer respond to infliximab 5 mg/kg, increasing the dose to 10 mg/kg is a costly decision with minimal gains in efficacy. Switching to adalimumab may be a preferred strategy since the infliximab dose escalation strategy produced an ICER of $332,032 per QALY, gaining only 0.03 QALYs (0.79 from 0.76). Of note, sensitivity analysis showed that reducing the cost of infliximab by one-third produced an ICER of $80,000 per QALY.

Yu et al[47] compared maintenance regimens of infliximab (5 mg/kg every 8 weeks) and adalimumab (40 mg every other week). A decision analytic model found that adalimumab-treated patients, compared to infliximab-treated patients, had 34%–40% lower hospital admission, longer remission periods (47.2% versus 37.1%), and lower overall costs (cost savings of $4,852) after a 56-week period.

SURGICAL TREATMENT

Most recent cost-analyses evaluating surgical interventions in IBD focus on colectomy and subsequent creation of an IPAA in UC patients. Results from the NORMAL survey[48] indicate that UC patients have an average of eight self-defined flares per year. Furthermore, the majority (62%) of patients report difficulty leading a normal life, while half (49%) of the patients report difficulty taking medications as prescribed every day. These findings strengthen the argument that earlier referral for curative colectomy may be of therapeutic benefit in patients with UC. Additional support was provided in a study by Ngyuen et al,[49] who created a Markov model to simulate a cohort of UC patients with newly diagnosed low-grade dysplasia. Immediate colectomy dominated all three of the enhanced surveillance strategies (repeated colonoscopy at 3, 6, and 12 months), yielding higher QALYs (20.1 versus 19.9 years) and lower costs ($75,900 versus $83,900). Sensitivity analysis was robust to various model parameters.

Subsequent IPAA is currently the standard of care for most UC patients after colectomy. Creation of a pouch forms a pseudo-rectum and eliminates the need for a permanent ostomy. This series of surgeries has become "modified" as a two-stage, instead of three-stage, procedure. Swenson et al[50] showed that the modified IPAA is

effective and cost-saving. Compared to the three-stage operation, the modified IPAA had equivalent clinical outcomes, measured by the number of bowel movements, fecal incontinence, and use of hypomotility medications. Total hospital costs for the modified group and the three-stage group were $27,270 and $38,184, respectively.

Holubar et al[51] demonstrated the economic benefit of UC patients undergoing total proctocolectomy in UC patients. Among the two groups, the mean cost of surgery/recovery period was $50,530 for IPAA ($n = 45$) and $39,309 for total proctocolectomy with Brooke ileostomy ($n = 15$). These patients incurred less cost after the curative procedure than before the surgery, with cost reductions for the 2 years after recovery of $9,296 in the IPAA group and $12,529 in the total proctocolectomy with Brooke ileostomy group.

COST OF NONADHERENCE

Two studies published during the last 2 years investigated the societal cost of nonadherence to 5-ASA therapy in UC patients. Higgins et al[52] conducted a systematic review of literature and unpublished randomized control trials evaluating the association of nonadherence to 5-ASA therapy with incidence of UC flares and healthcare costs. Those patients who were 5-ASA-adherent had 12.5% less comorbidity-adjusted annual cost of care than did nonadherent patients. The relative risk for UC flare in nonadherent versus adherent patients was 3.65 to infinity. Kane and Shaya[53] built a generalized linear model to associate nonadherence with higher medical costs. Data from the Maryland CareFirst BlueCross BlueShield program were analyzed using multivariate regression analysis. Nonadherence with 5-ASA was significantly associated ($P < 0.01$) with 2-fold increase in inpatient cost (22.8% versus 11.7%) and in increased utilization of outpatient services and office visits.

COST OF OPPORTUNITY LOSS

While our review has focused on the reporting the direct costs of IBD in the US, we should not overlook the indirect costs attributable to IBD, which remains difficult to analyze. One potentially quantifiable measure of indirect cost is work-related opportunity loss. It is estimated that the overall paid-employment burden of IBD in the US in 1998/1999 was more than $3.6 billion ($5,228 per person).[54] Discounted at a 3% rate to 2009 dollars, this represents an annual cost of $5.5 billion. Of note, clinical remission of CD is positively associated with increased probability of employment and improved mental and emotional well-being.[55,56]

CONCLUSIONS

IBD in the US represents two increasingly prevalent chronic diseases with considerable impact on healthcare expenditures. This review highlights key investigations that inform clinicians and policy makers of important factors and strategies to consider for optimization of resources in managing IBD.

Specifically, our review shows that clinicians should also be especially mindful when 1) ordering expensive diagnostic tests; 2) choosing lifetime maintenance medications; 3) escalating infliximab dosing for patients with loss of initial response; 4) considering benefits of earlier surgical referral for refractory UC; and 5) educating patients about the importance of adherence to therapy as it relates to clinical outcomes and costs. We have also summarized the importance of maximizing resource allocation during the first few years after IBD diagnosis, since this improves overall health outcomes and cost-effectiveness. Effective pediatric IBD management should be cost-saving in the long term since this population represents a longer duration of chronic disease and utilizes disproportionally more resources.

In the past, efficacious and cost-effective outpatient care of IBD patients resulted in fewer inpatient hospitalization, which drove total IBD costs. However, Kappelman et al[7] showed that while the advent of biologics has improved the quality of life for patients by decreasing hospitalization rates, the overall cost of IBD in the US remains relatively unchanged as outpatient costs have increased proportionally to the decrease in inpatient costs.

Future cost-effectiveness analyses are needed to consider the efficacy of biologics in the context of rising drug and administration costs in the US. Policies aimed at cost-containment for biologics may be necessary. Infliximab and adalimumab therapies have yet to be proven cost-effective in the US. In addition, it is not entirely clear which strategies are more efficacious and cost-effective in escalating or de-escalating (i.e., bottom-up or top-down) medical therapies for moderate to severe IBD.

Lastly, our review indicates that clinicians need to find a consensus which better defines medical therapy failure in IBD, especially UC. Outlining evidence-based protocols for surgical referral of IBD patients with medically refractory disease may improve patient quality of life and enhance cost-savings for both the individual and society. Further outcomes research indicating comparable long-term results with improving surgical techniques (e.g., colectomy with IPAA) would help to facilitate the transition from medical to surgical management of UC.

REFERENCES

1. Loftus EV. Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. *Gastroenterology*. 2004;126:1504–1517.
2. Kappelman MD, Rifas-Shiman SL, Kleinman K, et al. The prevalence and geographic distribution of Crohn's disease and ulcerative colitis in the United States. *Clin Gastroenterol Hepatol*. 2007;5:1424–1429.
3. Sewell JL, Yee HF Jr, Inadomi JM. Hospitalizations are increasing among minority patients with Crohn's disease and ulcerative colitis. *Inflamm Bowel Dis*. 2010;16:204–207.

4. Longobardi T, Jacobs P, Bernstein CN. Utilization of health care resources by individuals with inflammatory bowel disease in the United States: a profile of time since diagnosis. *Am J Gastroenterol*. 2004;99:650–655.
5. Yu AP, Cabanilla LA, Wu EQ, et al. The costs of Crohn's disease in the United States and other Western countries: a systematic review. *Curr Med Res Opin*. 2008;24:319–328.
6. Gibson TB, Ng E, Ozminkowski RJ, et al. The direct and indirect cost burden of Crohn's disease and ulcerative colitis. *Occup Environ Med*. 2008;50:1261–1272.
7. Kappelman MD, Rifas-Shiman SL, Porter CQ, et al. Direct health care costs of Crohn's disease and ulcerative colitis in US children and adults. *Gastroenterology*. 2008;135:1907–1913.
8. Kappelman MD, Porter CQ, Galanko JA, et al. Utilization of healthcare resources by U.S. children and adults with inflammatory bowel disease. *Inflamm Bowel Disease*. 2010 [Epub ahead of print].
9. Odes S, Vardi H, Friger M, et al. European Collaborative Study on Inflammatory Bowel Disease. Cost analysis and cost determinants in a European inflammatory bowel disease inception cohort with 10 years of follow-up evaluation. *Gastroenterology*. 2006;131:719–728.
10. Bernstein CN, Papineau N, Zajaczkowski J, et al. Direct hospital costs for patients with inflammatory bowel disease in a Canadian tertiary care university hospital. *Am J Gastroenterol*. 2000;95:677–683.
11. Hillson E, Dybicz S, Waters HC, et al. Health care expenditures in ulcerative colitis: the perspective of a self-insured employer. *Occup Environ Med*. 2008;50:969–977.
12. Bickston SJ, Waters HC, Dabbous O, et al. Administrative claims analysis of all-cause annual costs of care and resource utilization by age category for ulcerative colitis patients. *J Manag Care Pharm*. 2008;14: 352–362.
13. Cohen RD, Larson LR, Roth JM, et al. The cost of hospitalization in Crohn's disease. *Am J Gastroenterol*. 2000;95:524–530.
14. Silverstein MD, Loftus EV, Sandborn WJ, et al. Clinical course and costs of care for Crohn's disease: Markov model analysis of a population-based cohort. *Gastroenterology*. 1999;117:49–57.
15. Cohen RD, Waters HC, Tang B, et al. Effects of fistula on healthcare costs and utilization for patients with Crohn's disease treated in a managed care environment. *Inflamm Bowel Dis*. 2008;14:1707–1714.
16. Levesque BG, Cipriano LE, Chang SL, et al. Cost effectiveness of alternative imaging strategies for the diagnosis of small-bowel Crohn's disease. *Clin Gastroenterol Hepatol*. 2010;8:261–267.
17. Goldfarb NI, Pizzi LT, Fuhr JP Jr, et al. Diagnosing Crohn's disease: an economic analysis comparing wireless capsule endoscopy with traditional diagnostic procedures. *Dis Manag*. 2004;7:292–304.
18. Provenzale D, Wong JB, Onken JE, et al. Performing a cost-effectiveness analysis: surveillance of patients with ulcerative colitis. *Am J Gastroenterol*. 1998;93:872–880.
19. Provenzale D, Onken J. Surveillance issues in inflammatory bowel disease. *Ulcerative colitis. J Clin Gastroenterol*. 2001;32:99–105.
20. Rubenstein JH, Waljee AK, Jeter JM, et al. Cost effectiveness of ulcerative colitis surveillance in the setting of 5-aminosalicylates. *Am J Gastroenterol*. 2009;104:2222–2232.
21. Shen B, Shermock KM, Fazio VW, et al. A cost-effectiveness analysis of diagnostic strategies for symptomatic patients with ileal pouch-anal anastomosis. *Am J Gastroenterol*. 2003;98:2460–2467.
22. Parsi MA, Ellis JJ, Lashner BA. Cost-effectiveness of quantitative fecal lactoferrin assay for diagnosis of symptomatic patients with ileal pouch-anal anastomosis. *J Clin Gastroenterol*. 2008;42:799–805.
23. Available at: http://www.drugstore.com/pharmacy/prices/drugprice.asp?ndc=00149075215&trx=1Z5006
24. Nikfar S, Rahimi R, Rezaie A, et al. A meta-analysis of the efficacy of sulfasalazine in comparison with 5-aminosalicylates in the induction of improvement and maintenance of remission in patients with ulcerative colitis. *Dig Dis Sci*. 2009;54:1157–1170.
25. Mackowiak JI. A two-stage decision analysis to assess the cost of 5-aminosalicylic acid failure and the economics of balsalazide versus mesalamine in the treatment of ulcerative colitis. *Manag Care Interface*. 2006;19:39–46,56.
26. Buckland A, Bodger K. The cost-utility of high dose oral mesalazine for moderately active ulcerative colitis. *Aliment Pharmacol Ther*. 2008;28:1287–1296.
27. Akobeng AK, Gardener E. Oral 5-aminosalicylic acid for maintenance of medically-induced remission in Crohn's disease. *Cochrane Database Syst Rev*. 2005;1:CD003715.
28. Dubinsky MC, Reyes E, Ofman J, et al. A cost-effectiveness analysis of alternative disease management strategies in patients with Crohn's disease treated with azathioprine or 6-mercaptopurine. *Am J Gastroenterol*. 2005;100:2239–2247.
29. Waljee AK, Joyce JC, Wang S, et al. Algorithms outperform metabolite tests in predicting response of patients with inflammatory bowel disease to thiopurines. *Clin Gastroenterol Hepatol*. 2010;8:143–150.
30. 2006 Drug topics, red book. Montvale, NJ: Medical Economics; 2006.
31. Ollendorf DA, Lidsky L. Infliximab drug and infusion costs among patients with Crohn's disease in a commercially-insured setting. *Am J Ther*. 2006;13:502–506.
32. Hanauer SB, Feagan BG, Lichtenstein GR, et al. ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet*. 2002;359:1541–1549.
33. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2005; 353:2462–2476.
34. Thomas T, Cohen RD. Pharmacoeconomic considerations for inflammatory bowel disease in the era of biological therapies. *Expert Rev Gastroenterol Hepatol*. 2007;1:101–112.
35. Irving PM, Gibson PR. Infliximab: getting the most for your money. *J Gastroenterol Hepatol*. 2007;22:1559–1561.
36. Cohen RD, Thomas T. Economics of the use of biologics in the treatment of inflammatory bowel disease. *Gastroenterol Clin North Am*. 2006;35:867–882.
37. Jaisson-Hot I, Flourié B, Descos L, et al. Management for severe Crohn's disease: a lifetime cost-utility analysis. *Int J Technol Assess Health Care*. 2004;20:274–279.
38. Saro C, da la Coba C, Casado MA, et al. Resource use in patients with Crohn's disease treated with infliximab. *Aliment Pharmacol Ther*. 2007;26:1313–1323.
39. Lindsay J, Punekar YS, Morris J, et al. Health-economic analysis: cost-effectiveness of scheduled maintenance treatment with infliximab for Crohn's disease—modelling outcomes in active luminal and fistulizing disease in adults. *Aliment Pharmacol Ther*. 2008;28:76–87.
40. Tsai HH, Punekar YS, Morris J, et al. A model of the long-term cost effectiveness of scheduled maintenance treatment with infliximab for moderate-to-severe ulcerative colitis. *Aliment Pharmacol Ther*. 2008; 28:1230–1239.
41. Arseneau KO, Cohn SM, Cominelli F, et al. Cost-utility of initial medical management for Crohn's disease perianal fistulae. *Gastroenterology*. 2001;120:1640–1656.
42. Condino AA, Fidanza S, Hoffenberg EJ. A home infliximab infusion program. *J Pediatr Gastroenterol Nutr*. 2005;40:67–69.
43. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology*. 2007;132:52–65.
44. Wu EQ, Mulani PM, Yu AP, et al. Loss of treatment response to infliximab maintenance therapy in Crohn's disease: a payor perspective. *Value Health*. 2008;11:820–829.
45. Schnitzler F, Fidder H, Ferrante M, et al. Long-term outcome of treatment with infliximab in 614 patients with Crohn's disease: results from a single-centre cohort. *Gut*. 2009;58:492–500.
46. Kaplan GG, Hur C, Korzenik J, et al. Infliximab dose escalation vs. initiation of adalimumab for loss of response in Crohn's disease: a cost-effectiveness analysis. *Aliment Pharmacol Ther*. 2007;26: 1509–1520.
47. Yu AP, Johnson S, Wang ST, et al. Cost utility of adalimumab versus infliximab maintenance therapies in the United States for moderately to severely active Crohn's disease. *Pharmacoeconomics*. 2009;27: 609–621.
48. Rubin DT, Siegel CA, Kane SV, et al. Impact of ulcerative colitis from patients' and physicians' perspectives: Results from the UC: NORMAL survey. *Inflamm Bowel Dis*. 2009;15:581–588.
49. Nguyen GC, Frick KD, Dassopoulos T. Medical decision analysis for the management of unifocal, flat, low-grade dysplasia in ulcerative colitis. *Gastrointest Endosc*. 2009;69:1299–1310.

50. Swenson BR, Hollenbeak CS, Poritz LS, et al. Modified two-stage ileal pouch-anal anastomosis: equivalent outcomes with less resource utilization. *Dis Colon Rectum*. 2005;48:256–261.
51. Holubar SD, Long KH, Loftus EV Jr, et al. Long-term direct costs before and after proctocolectomy for ulcerative colitis: a population-based study in Olmsted County, Minnesota. *Dis Colon Rectum*. 2009;52:1815–1823.
52. Higgins PD, Rubin DT, Kaulback K, et al. Systematic review: impact of non-adherence to 5-aminosalicylic acid products on the frequency and cost of ulcerative colitis flares. *Aliment Pharmacol Ther*. 2009;29:247–257.
53. Kane S, Shaya F. Medication non-adherence is associated with increased medical health care costs. *Dig Dis Sci*. 2008;53:1020–1024.
54. Longobardi T, Jacobs P, Bernstein CN. Work losses related to inflammatory bowel disease in the United States: results from the National Health Interview Survey. *Am J Gastroenterol*. 2003;98:1064–1072.
55. Lichtenstein GR, Yan S, Bala M, et al. Remission in patients with Crohn's disease is associated with improvement in employment and quality of life and a decrease in hospitalizations and surgeries. *Am J Gastroenterol*. 2004;99:91–96.
56. Longobardi T, Jacobs P, Wu L, et al. Work losses related to inflammatory bowel disease in Canada: results from a National Population Health Survey. *Am J Gastroenterol*. 2003;98:844–849.

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