

Managing Costs and Care for Chronic Idiopathic Constipation

Dana McCormick, RPh

Introduction

Globally, chronic idiopathic constipation (CIC) is one of the most common chronic functional gastrointestinal (GI) disorders encountered by clinicians and has been so for decades. Constipation continues to be a prevalent condition and despite some effective treatments, it negatively affects patients' quality of life (QOL). Approximately 1 in 6 Americans have CIC,^{1,2} similar to the number of Americans who develop foodborne illnesses annually³ and the number of Americans who have elevated total cholesterol.⁴ Despite the wide variety of available treatments, CIC often poses a clinical conundrum. Effective treatment depends on a rational approach, use of efficacious interventions, and an assessment of cost-effectiveness. In addition, patients need to make significant lifestyle changes and be invested in ongoing treatment to ensure successful outcomes. CIC continues to be associated with significant costs, primarily in the outpatient areas of imaging and procedures.⁵ CIC, like many other common conditions, may contribute to greater morbidity and healthcare costs.

Prevalence

CIC's incidence is difficult to determine; results of studies conducted in the 1990s indicated that 2% to 27% of North Americans experienced chronic constipation (CC).⁶⁻⁸ Experts tend to rely on 2 studies for rough estimates of prevalence and incidence of CC. Statisticians conducted a population-based study between 1998 and 2003 that documented a cumulative incidence of 17.4%, noting that approximately 1 in 6 individuals reported having CC. Women and elderly persons were more likely to be affected.¹ Results of a 2011 study indicated that CIC's global prevalence is between 1.9% and 40.1%, with a mean of approximately 14%.⁹ Additionally, results of studies show the epidemiology of disease burden and indicate that women, older age, lower socioeconomic status, reduced caloric intake, sedentary lifestyle, and reduced dietary fiber intake are factors for an elevated risk of CIC.¹⁰⁻¹²

Comorbidities

Several investigative researchers have tried to determine which comorbidities are likely to occur with CIC. A meta-analysis of

ABSTRACT

For decades, chronic idiopathic constipation (CIC) has been one of the most common chronic functional gastrointestinal disorders encountered by clinicians. Common comorbidities include depression, diabetes, functional dyspepsia, hypothyroidism, overweight, obesity, and neurological disorders. CIC imposes a large economic burden on the American healthcare system with estimated costs of \$1912 to \$7522 in 2007 US dollars per patient per year. Individuals affected by CIC indicate significant rates of absenteeism and presenteeism at work. Those with constipation have poorer general health, mental health, and social functioning compared with healthy controls. The average patient with CIC tries approximately 4 over-the-counter (OTC) and 2 prescription medications before finding an effective treatment. Guideline-directed treatment generally recommends moving from lifestyle modifications to OTC products and prescription laxatives. Most patients report that the relief they receive is unacceptable. Reliable evidence indicates that newer prescription drugs offer greater relief of symptoms than those of traditional approaches. Appropriate formulary management of CIC offers opportunities to impact patient care in 3 major areas: clinical, economic, and humanistic outcomes. Plans will need to be flexible, especially because patient dissatisfaction with treatment is prevalent in CIC.

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35 studies identified increased incidences of depression, diabetes, functional dyspepsia, overweight, and obesity.¹⁰ Results of another study, which included 28,854 individuals with CC in a US health insurance database, found increased rates of depression and mood disorders (14.2%), hypothyroidism (9.8%), and other neurological disorders (9.7%) in patients with constipation compared with nonconstipated controls.¹³ A smaller questionnaire survey (N = 307 patients with CC and 307 matched controls) showed a significantly increased prevalence of Parkinson disease (4%), moderately elevated metabolic disorders, and other neurological diseases. However, CC was not associated with GI pathology.¹⁴ Results of a recent study looking at the prevalence of CIC in patients enrolled in the Rochester Epidemiology Project indicated a significant association between multiple sclerosis and CIC.¹⁵

Direct and Indirect Costs

CIC's economic burden on the American healthcare system is significant, and investigators report widely varying direct costs. However, estimates of \$1912 to \$7522 per patient per year in 2007 US dollars have been generally accepted. A limitation of this study was that it lacked disorder-specific diagnostic coding, and some subjects

may have been misclassified.¹⁶ The costs and healthcare utilization associated with patients who have CC (Table 1^{8,17-24}) are indicators that the disease deserves more attention in the healthcare setting.

Results of a 2013 study of patients with CC (N = 14,854 with patients split equally between the active constipation and control groups) showed that mean annual all-cause costs were close to \$12,000 annually.²⁵ Roughly 81% of costs were associated with use of medical services (eg, visits to prescribers and outpatient services). Pharmacy costs in the active constipation arm were \$1830 compared with \$1162 in the control arm. It was found that pharmacy costs for patients who reported CC with abdominal symptoms were 1.6 times higher than in patients who did not have abdominal symptoms. The investigators note, with caution, that the cost of CC is comparable to that of migraine and exceeds that attributed to asthma. They also suggest that CC consumes more healthcare dollars than most payers are aware of, mainly because payers have heightened awareness of other chronic conditions.²⁵

Investigators from Mayo Clinic and South Dakota State University recently compared long-term healthcare resource utilization (HCRU) costs associated specifically with patients with CIC (n = 365) and patients with irritable bowel syndrome with constipation (IBS-C; n = 115), with community-based matched controls (n = 730). Of note, these investigators did not include the costs of prescription or over-the-counter (OTC) medications. This study was part of the Rochester Epidemiology Project, a collaboration of clinics, hospitals, and other medical facilities in Minnesota and Wisconsin, involving community members who agreed to share their medical research. Patient demographics were congruent with previous studies; the average age was 66 years for patients with CIC, patients were primarily white, and 63.9% of patients were female. Over the 2 years, mean outpatient costs, which were adjusted for age, gender, GI symptoms, and comorbidities, were \$6284 in 2011 US dollars for CIC without medications. Costs among the matched community control were \$5254,¹⁵ indicating that CIC can be quite costly for healthcare systems.

These investigators conducted a follow-up analysis at 10 years. Individuals with CIC had higher adjusted mean costs than controls, but the difference did not reach statistical significance. Patients with CIC had significantly higher procedure costs.¹⁵ This indicates that patients with CIC consume more healthcare resources than matched control patients, especially earlier in the course of the disease, but over a decade, the costs are similar to those of matched controls.

Indirect Costs: Growing Evidence

Few studies documenting indirect costs of constipation have been conducted in the United States, but interest is growing, as is associated evidence. Educating healthcare professionals regarding the extensive impact of CIC on patients could be motivational to address the needs of patients with CIC more proactively. Improving

TABLE 1. Summary of Costs Associated With Chronic Constipation^{8,17-24}

- Constipation is 1 of 5 most common physician outpatient diagnoses in the United States.
 - 22% of Americans who have constipation seek help from a healthcare provider.
- The annual direct medical costs for constipation were recently estimated to exceed \$230 million, and the costs incurred by women with constipation were double that of women without constipation. The direct costs over 15 years were \$64,000 per person with constipation versus \$26,000 without constipation.
- Americans spent more than \$800 million on laxatives in 2007.
- Constipation is associated with 8 million physician office visits annually.
- Between 2006 and 2011, constipation-related ED visits increased by 41.5% and costs associated with these visits increased 121.4%.
 - 14% of patients with chronic idiopathic constipation report 1 ED visit annually.
- Inpatient admissions are increasing, especially in a younger cohort of patients.
 - In 2010, US hospital costs linked to constipation were \$4.25 billion.
- Patients with chronic constipation are associated with a higher incidence and prevalence of benign colorectal neoplasm and colorectal malignancy.

ED indicates emergency department.

provider–patient communication could help improve patient outcomes, as there appears to be a disconnect between what providers perceive and patient experience. American investigators conducted the BURDEN-CIC study from June 2016 through January 2017 to clarify the experiences and ongoing needs of patients with CIC. Investigators also assessed the alignment of perceptions and needs with those of healthcare providers. This study included 1223 respondents who reported an average duration of CIC of 4 years, with median onset at age 44 years. With regard to personal activities (eg, social gatherings, sporting events, family activities, hobbies), CIC interfered with these activities 4 days per month in 60% of respondents. One-fourth of patients reported that they missed roughly 60 days of work or school per year, which is an annual productivity loss of 23%.²¹

Results of a recent study from Italy (N = 828) found that patients who reported the most severe constipation had productivity losses similar to those reported by patients with ankylosing spondylitis and major depression. Those with the mildest symptoms had productivity losses of 16%, which is the approximate rate reported by patients with obesity, diabetes, and gastroesophageal reflux disease. Patients with the mildest symptoms reported sick leave use equivalent to \$676 annually and presenteeism (impaired productivity while at work) costs of \$3886 annually. Those with the most severe constipation reported sick leave use equivalent to \$3948 annually and presenteeism costs of \$9203 annually. Investigators calculated the potential impact of effective therapy on productivity and found that for each 20% decrease in constipation severity, employers would save between \$641 and \$2437 per employee.²⁶

Quality of Life

QOL encompasses a number of different factors and contributes to patient satisfaction and outcomes. Completing activities of daily living, seeing friends and family, and enjoying meals keep morale high, influencing patients' outlook and adherence. Patients experiencing psychological effects from CIC may experience further negative impact if treatment begins and is accompanied by AEs.²¹

Meta-analysis has found that people with constipation have poorer general health, mental health, and social functioning compared with healthy controls. These AEs are greater in hospitalized patients, with investigators reporting mental and physical subcomponent scores comparable to those of patients with unstable IBS and functional dyspepsia. Among people in the community studies in the meta-analysis, mental and physical mean scores were comparable to those of patients with chronic allergies, dermatitis, diabetes, and stable ulcerative colitis.²⁷

The market research firm Harris Poll surveyed 250 gastroenterologists and 881 patients with CIC on behalf of Shire between April 16, 2018, and June 6, 2018, for the Current Insights about Constipation Survey.²⁸ The survey confirmed what other studies

have found: patients with CIC experience considerable frustration and stress. The gastroenterologists who responded indicated that the average patient with CIC tries approximately 4 OTC and 2 prescription medications before finding an effective treatment. **Table 2**²⁸ lists additional findings.

Effective Treatment and Outcomes

Real-world effectiveness of common treatments is an important consideration when making decisions for health systems and individual patients. Fiber is often the first intervention recommended for CIC. Two systematic reviews have looked at randomized controlled trials of soluble and insoluble fiber. Results of 1 study found limited benefit, overall, in CIC but suggested that soluble fiber was more effective than placebo and ameliorated individual symptoms.²⁹ Results of another study found soluble fiber effective for CIC but stressed its propensity to cause unwanted GI AEs, including flatulence.³⁰ Data show that CIC cannot be treated successfully by increasing water intake in the absence of dehydration. Few studies have looked at hydration alone.^{31,32}

Meta-analysis indicates that bisacodyl, linaclotide, lubiprostone, polyethylene glycol, prucalopride, and sodium picosulfate were all more effective than placebo for CIC, but data to support the efficacy of lactulose were limited. Investigators noted that diarrhea was significantly more common in patients assigned to laxatives and pharmacologic therapies.³³ Currently, 4 additional prescription drugs are available: the prosecretory drugs

TABLE 2. Findings from the Current Insights About Constipation Survey²⁸

- 75% of people with CIC spend ≥1 hour using the toilet daily.
- 9% spend 3 to 4 hours and 10% spend ≥5 hours on the toilet on average daily.
- 84% of respondents indicated that others underestimate CIC's negative impact on their everyday life.
- 71% of respondents reported that CIC interferes with enjoyable activities (eg, family functions, children's school or sporting events).
- On average, people diagnosed with CIC missed 7 workdays, 5 social events, and 4 of their children's events in the previous year.
- Patients with CIC indicated that it has negatively affected their self-confidence (60%), ability to engage in hobbies they enjoyed in the past (59%), partnership relationships and intimacy (54%), and job/career or ability to work (47%).
- Respondents had experienced CIC symptoms for an average of 2.7 years before receiving a diagnosis, and 56% reported making about 5 visits to a healthcare provider before definitive diagnosis.

CIC indicates chronic idiopathic constipation.

lubiprostone, linaclotide, and plecanatide, and the selective 5-HT₄ receptor agonist, prucalopride.

Few studies have been conducted on CIC that address the cost-effectiveness of newer drugs:

- A 2016 study used a decision tree modeling technique, hypothesizing treatment over 4 weeks, comparing linaclotide with lubiprostone in the treatment of adult patients with CIC. Investigators determined that linaclotide was less costly than lubiprostone with similar effectiveness for patients with CIC.³⁴
- A 2018 study, using a cohort state-transition model, evaluated the cost-effectiveness of lubiprostone, prucalopride, placebo, and immediate referral to secondary care in CIC. Based in the United Kingdom, investigators found that over a 10-year period, lubiprostone may be cost-effective compared with prucalopride or immediate referral. It was not cost-effective compared with placebo.³⁵

Both of these studies were model based, an approach used when trials are not feasible. Although they incorporated information from multiple sources and could provide head-to-head comparison, they relied on simplified assumptions, which may have been flawed.³⁶

Surgical Candidates

Very few patients have surgically correctible constipation. Surgery should be reserved for rare, severe, and refractory cases of constipation and considered only after preoperative evaluation that includes imaging techniques and manometric findings, revealing colonic inertia (slow transit). Usually, the surgical candidate will have neuropathy and/or myopathy involving the entire colon.³⁷ Patients with dyssynergia (anorectal obstruction or abnormal coordination of pelvic and abdominal muscles) usually report excessive straining, feelings of incomplete evacuation, and manual maneuvering for a bowel movement. They, too, may be considered for surgery.³⁸

Patients who have persistent, intractable slow transit constipation are sometimes considered for a total colectomy with ileostomy or subtotal colectomy with ileorectal anastomosis. Postsurgical complications may include small bowel obstruction, recurrent or persistent constipation, diarrhea, and incontinence. Surgery generally is not recommended for constipation caused by anorectal dysfunction.³⁹ Use of implantable devices that provide sacral stimulation is under further investigation.⁴⁰⁻⁴²

Impact of Failure to Treat

Value is a constant concern in healthcare. The cost of the treatment of CIC must be compared with the value of successful outcomes or the cost of failure to treat CIC. Failing to treat CIC can cause or contribute to higher costs in several ways.

Currently, little research has documented the secondary care costs of untreated constipation, although most clinicians are

aware that untreated constipation can progress to pain, discomfort, impaction, and incontinence, and increases the likelihood of hospitalization. Results of a recent study showed that approximately half of patients treated for fecal impaction have experienced CC. The investigators documented complications, categorizing the type of adverse outcome based on the presence or absence of GI tract damage. Most often, patients developed intestinal perforation, obstruction, or stercoral (consisting of or containing feces) ulcers in the GI tract. Outside the GI tract, obstructive uropathy was most common.⁴³

A review of treatments for CC, published by the American Board of Family Medicine, recommended that family physicians consider the patient's view of the condition and weigh the costs and benefits of diagnostic tests and treatments. This review indicates that untreated CC can cause or exacerbate hemorrhoids, anal fissures, organ prolapse, fecal incontinence, fecal impaction, and bowel obstruction. It may also cause bowel perforation and stercoral peritonitis.⁴⁴

Formulary Management at the Plan Level

Constipation is often considered a benign condition that responds well to simple interventions, but this is a common misconception among healthcare providers and patients. As described above, it is often associated with multiple complications and affects QOL.⁴⁵ Healthcare systems should be observing their prescribers' behavior carefully when making formulary decisions.

A survey of more than 848 US gastroenterologists identified trends related to treatment of CC, described as "potentially actionable."⁴⁶ Survey respondents tended to use OTC rather than prescription treatments. In fact, gastroenterologists recommended OTC treatments (fiber supplements, osmotic laxatives, stimulants, and stool softeners) as first-line therapy for patients with CC more than 95% of the time in keeping with existing guidelines. Just 3% of gastroenterologists recommended a prescription medication (lactulose, sorbitol, linaclotide, or lubiprostone) as first-line therapy. If patients failed to improve, 70% of gastroenterologists continued to employ OTC treatments, and 30.3% recommended a prescription option as their second-line treatment of choice.⁴⁶ This raises a question: Could earlier, more aggressive treatment avoid adverse outcomes, increase patient satisfaction, and ultimately save money?

Results of the BURDEN-CIC study showed that 16% of patients indicated they were currently taking a prescription treatment for their CIC. Of those who were taking a prescription product, 41% reported being satisfied or completely satisfied with their branded prescription medication, which the investigators interpreted as meaning that 59% of patients with CIC may be looking for new treatment options. Dissatisfaction was usually associated with lack of efficacy (55%) and presence of AEs (35%). Generally, patient expectation was a concern; for example, 57% expected

prescription medications to work within 24 hours, but just 26% reported relief within 1 day. Most patients reported that prescription therapy relieved symptoms within approximately 3 days.²¹ Healthcare systems and healthcare providers need to be aware of—and manage—patient expectations.

In addition, the BURDEN-CIC study results found that patients and healthcare providers were frustrated with available options for CIC. They also reported that AEs (primarily diarrhea) negatively affected treatment satisfaction, as AEs interfered with activities of daily living. All participants identified treatment-related diarrhea as an unacceptable treatment outcome. Perhaps the most important finding of this study was that patients tended to accept CIC as part of their daily lives, but healthcare providers perceived that patients fixated on CIC symptoms.²¹

Making Formulary Decisions

Appropriate formulary management of CIC offers opportunities to have an impact on patient care in 3 major areas: clinical, economic, and humanistic outcomes. CIC can be physically and psychologically draining for patients. It impacts not only the patient's QOL, but may also have economic effects, both on the cost of therapy and the cost of therapy failure. Managed care plans need strategies to ensure that patients with CIC receive appropriate medication that addresses constipation proactively.

In addition, it is important for healthcare administrators and providers to understand patients' perceptions of care. Results of a survey of 557 American patients who self-identified with constipation found that almost all of them (96%) had used constipation-relief therapy. Yet, 47% were not completely satisfied, citing either lack of efficacy (82%) or safety concerns (16%). These investigators summarized their findings by citing 3 important observations³⁸:

- When patients reported a symptom as bothersome, often that symptom was also the most severe for them.
- As the duration of constipation increases, patients were likely to develop additional symptoms, and preexisting symptoms became more severe and bothersome.
- Fiber, OTC products, and prescription laxatives did not deliver the results the patients desired.

It is important to note that this survey was conducted before the approval of some of the new prescription agents. Regardless, these observations have clinical implications that should be considered when making formulary decisions. It is critical to understand that constipation is not just 1 simple condition; constipation differs based on the patient's unique underlying pathophysiologic mechanism and the likelihood that patients may have overlapping pathophysiologic contributors. Patients with CIC could often benefit from more aggressive therapy, including providing patient access to prescription products.

Guideline-Directed Treatments

Combined, the patient outcomes and cost data call for systematic approaches, including guideline-directed care, if available, that ensure effective drugs are available and can be used appropriately. Understanding CIC, its direct and indirect fiscal consequences, and the medications used to prevent and treat it ensures that the organization's rationale is clinically and fiscally sound.

Many managed care organizations use guidelines to direct therapy, improve outcomes, and manage medication costs. Typical formulary processes rely on examining the rationale for inclusion/exclusion in the guidelines and determining cost-effectiveness. The general assumption is that evidence-based guidelines will lead to better overall outcomes, reduce costs, and provide the value that patients and the system are seeking. However, that is not always the case. Health systems need to galvanize their pharmacy and therapeutics committees to weigh real-world effectiveness, safety, cost, and outcomes to provide the most value to their patients.⁴⁷ The use of evidence-based guidelines is often being supplemented with data gained from real-world evidence by P&T committees to help create effective policies. Most CIC guidelines are slightly outdated at this point, so plans cannot rely completely on these documents to assist with formulary decision making. Prescribers then must rely on experience and local/organization guidance when choosing prescription approaches. **Table 3**⁴⁸⁻⁵¹ lists the available, but not necessarily current, evidence-based guidelines for CIC.

Moving Toward Prescription Drug Therapy

Most experts and guidelines recommend certain basic approaches to treat constipation (**Figure 2**⁴⁸⁻⁵¹). For the newer prescription medications, prior authorization forms tend to be similar among insurers and ask for the patient's age, with restricted use to adults, and a confirmed diagnosis. Prescribers may also have to confirm the candidate's lack of response to maximum tolerated doses of osmotic laxatives and rule out GI obstruction. Some are more detailed, asking about dietary measures and stimulant laxatives, or requiring a consultation with an appropriate specialist.

In Canada, a task force evaluated specialists' practice patterns and developed a treatment algorithm. The task force found that although specialists tend to use a stepwise approach to constipation and CIC, specialists reported that referring physicians might not employ a stepped approach, leading to suboptimal outcomes and unnecessary referrals. Specialists also perceived that when OTC products fail to provide symptomatic relief, primary care providers and patients seem to be hesitant to progress to prescription drugs. The task force postulates access, cost, prescriber experience and knowledge about newer treatment options, patient perception about prescription medications, and treatment schedules may be barriers.⁴⁸

TABLE 3. Guidelines for the Treatment of Chronic Idiopathic Constipation⁴⁸⁻⁵¹

American Gastroenterological Association medical position statement on constipation	Bharucha AE, Dorn SD, Lembo A, Pressman A; American Gastroenterological Association. <i>Gastroenterology</i> . 2013;144(1):211-217. doi: 10.1053/j.gastro.2012.10.029.
American College of Gastroenterology monograph on the management of irritable bowel syndrome and chronic idiopathic constipation	Ford AC, Moayyedi P, Lacy BE, et al; Task Force on the Management of Functional Bowel Disorders. <i>Am J Gastroenterol</i> . 2014;109(suppl 1):S2-S26. doi: 10.1038/ajg.2014.187.
Constipation in older people: a consensus statement	Emmanuel A, Mattace-Raso F, Neri MC, Petersen KU, Rey E, Rogers J. <i>Int J Clin Pract</i> . 2017;71(1).
Treatment algorithm for chronic idiopathic constipation and constipation-predominant irritable bowel syndrome derived from a Canadian national survey and needs assessment on choices of therapeutic agents	Tse Y, Armstrong D, Andrews CN, et al. <i>Can J Gastroenterol Hepatol</i> . 2017;2017:8612189. doi: 10.1155/2017/8612189.

products become available. Also, as guidelines and newer data become available, payers will evolve their management strategies.

Conclusions

CIC is complicated, and many of the treatment approaches clinicians have used, and believed in, for decades do not deliver the results patients need. Untreated, CIC can create significant downstream problems. In the past decade, the FDA has approved several new treatment options that are more effective than simple lifestyle changes and OTC drugs. Earlier consideration of pharmacologic intervention can help patients improve QOL and avoid adverse outcomes. ■

Author affiliation: Director of Pharmacy, Blue Cross Blue Shield of Texas, Richardson, TX.

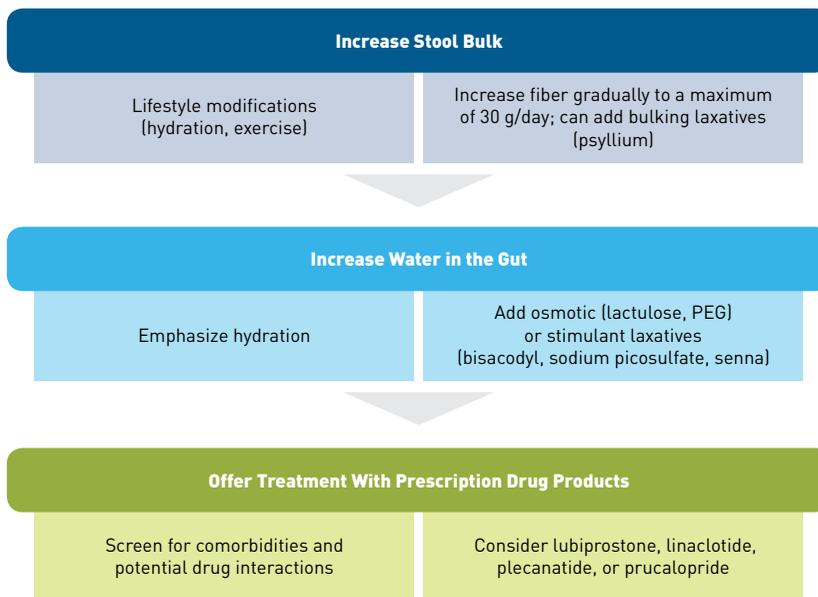
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Address correspondence to: dana_mccormick@bcbstx.com.

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FIGURE. Basic Management of Constipation^{2,48-51}

PEG indicates polyethylene glycol.

Fortunately, more effective treatments are available for patients with CIC than ever before. With the approval of new drugs in this space, guidelines may not be up-to-date, which leaves prescribers and managed care plans possibly not finding the targeted guidance they want or need. Current formulary management strategies have mainly included identification of preferred products based on pricing. Plans may evolve this approach in the near future as more

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