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## The Cost of Inflammatory Bowel Diseases in High-Income Settings

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| **Abstract:** | The cost of caring for patients with inflammatory bowel diseases (IBDs) continues to increase worldwide. The cause is not only a steady increase in the prevalence of Crohn's disease (CD) and ulcerative colitis (UC) in both developed and newly industrialized countries, but also the chronic nature of the diseases, the need for long-term, often expensive treatments, the use of more intensive disease monitoring strategies, and their impact on work productivity. This Commission draws together a wide range of expertise to discuss the current costs of IBD care, the drivers of increasing costs, as well as how to deliver affordable care for IBD in the future. The key conclusions are that (i) increases in health care costs must be evaluated against improved disease control and reductions in indirect costs, and (ii) that overarching systems for data interoperability, registries, and big data approaches must be established for continuous assessment of effectiveness, costs, and cost-effectiveness of care. International collaborations should be sought in order to evaluate novel models of care (such as value-based health care, including integrated health care and participatory health care models), as well as to improve the education and training of clinicians, patients, and policymakers. |

## Title

The Costs of Inflammatory Bowel Diseases in High-Income Settings

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# ABSTRACT

The cost of caring for patients with inflammatory bowel diseases (IBD) continues to increase worldwide. The cause is not only a steady increase in the prevalence of Crohn's disease and ulcerative colitis in both developed and newly industrialized countries, but also the chronic nature of the diseases, the need for long-term, often expensive treatments, the use of more intensive disease monitoring strategies, and the impact of the diseases on economic productivity. This report draws together a wide range of expertise to discuss the current costs of IBD care, the drivers of increasing costs, and how to deliver affordable care for IBD in the future. The key conclusions are that (i) increases in health care costs must be evaluated against improved disease management and reductions in indirect costs, and (ii) that overarching systems for data interoperability, registries, and big data approaches must be established for continuous assessment of effectiveness, costs, and the cost-effectiveness of care. International collaborations should be sought out in order to evaluate novel models of care (such as value-based health care, including integrated health care and participatory health care models), as well as to improve the education and training of clinicians, patients, and policymakers.

# 1. INTRODUCTION

Crohn's disease and ulcerative colitis, together known as inflammatory bowel diseases (IBD), affect approximately seven million people globally.[1] A recent report from the Global Burden of Disease Study described a surge in IBD incidence in emerging countries and a steady prevalence in developed countries. As such, the number of patients living with IBD will continue to grow, with a prevalence rate forecast to approach 1% within the next ten years in some regions.[2] Due to IBD's incurability and unpredictable disease course, lifelong monitoring and treatment are often required to prevent disease progression and complications that impair patients' quality of life and ability to work.[3]

The continuing rise in IBD prevalence and aging populations worldwide will inevitably lead to an increasing use of health care resources by patients with IBD. In parallel with these trends, continuing innovations in IBD therapeutics, diagnostics, and preventatives are creating more options for reducing the disease burden. The increasing availability of biological agents and small molecules marks the beginning of a new era in the management of IBD, as early, aggressive treatment and treat-to-target become more common.[4,5] These trends will all place a burden on health care systems and require that we identify modifiable cost drivers and develop strategies for delivering equitable and affordable IBD care for all patients.

Meanwhile, wide variations in social support systems and rules for reimbursement across countries hinder efforts to estimate the global cost burden of IBD. For instance, the US ranks higher in health care spending per capita than other Western countries and this is partially explained by a lack of central regulation of drug prices, something that is certainly affecting US data for IBD care.[6] The lack of transparency in drug pricing and the paucity of data about indirect costs, such as productivity losses and work disability among IBD patients, further distort our estimations of costs and cost-effectiveness.

The *Lancet Gastroenterology & Hepatology* Commission, consisting of a diverse faculty of health care professionals with expertise in the field of IBD and health economists, was formed to deliver an extensive summary of the literature and discuss key topics on the costs and cost-effectiveness of treating IBD currently, and how it is likely to look in the future. Furthermore, we offer suggestions for how to deliver more affordable IBD care. The report's focus is on high-income countries in Europe, North America, Australia and New Zealand, and Asia. While the burden, and hence the costs, of IBD will increase significantly in low- and middle-income countries in the future as the incidence of IBD increases,[2] important differences between these countries in their social, health care, and economic structures means they are best discussed separately.

# 2. How Expensive Is IBD Care Now and How Expensive Will it Be in the Future?

## 2.1 A Framework for Understanding IBD-related Costs

The total cost of a chronic disease like IBD can be separated into direct costs (those incurred as a result of providing health care specifically targeting symptoms, signs, and sequelae) and indirect costs (those incurred by patients not directly related to the receipt of health care, and the impact that IBD and its sequelae have on economic productivity). The total cost of IBD can be understood as an interplay between four factors: (1) overall disease burden; (2) treatment and monitoring of IBD and related complications; (3) access to, and utilization of, IBD-specific medical care; and (4) impact of the disease on patients' ability to contribute economically.

### 2.1.1 Disease Burden

The concept of burden refers to the negative effects that living with a disease has on a person's state of well-being, physical health, and health-related quality of life. The disease burden across a population is a function of the prevalence of the disease and its severity among those living with the disease. Disease burden is the main driver of both direct and indirect costs, in that it prompts health care-seeking behaviour (which is responsible for the direct costs) and to the extent to which it causes disability, impairment, or death, which limits the patients ability to contribute to society (its indirect costs).

Currently, in the industrialized West, there is a compounding prevalence of IBD, whereby the number of people living with it is steadily increasing due to the nature of IBD as a chronic disease in which incidence greatly surpasses mortality.[7] The prevalence of IBD is anticipated to continue to rise throughout the world, even in countries where IBD has been uncommon until recently.[2] The prevalence of IBD can be lowered either by reducing the incidence of IBD through identifying and eliminating etiological factors, or by shortening disease duration by finding a cure or delaying the onset of disease. Similarly, the burden of IBD can be ameliorated through developing and implementing effective therapies that reduce disease severity or prevent complications and comorbidities, e.g., mental health issues such as anxiety and depression, and by improving methods for earlier detection and close monitoring for complications.[8] Table 1 offers a summary of these demographic, behavioural, and disease-related characteristics.

### 2.1.2 Direct Costs of Care

Defined broadly, the direct costs of care are the amount of money spent by individual patients and health care systems on services. The monetary costs of these services vary considerably depending on the country or region. This variability in direct costs between different countries is the result of several factors. The wealth of a country, and the resources it allocates to support the health of its citizens, affects the types of services that can be provided and the extent to which they are accessed by patients. The costs of developing and maintaining the infrastructure for delivering health care also varies considerably; this includes, but is not limited to, the costs of educating practitioners and support staff; the costs of developing facilities, medical equipment, and drugs; and the profits and wages paid to individuals and corporations for continued care and innovation.

In addition, governments and insurers differ in the extent to which they regulate the health care market through capping drug prices or reimbursing physicians, which further affects the costs of care. The demand for health care services is also partially determined by the demographics and disease behaviour in the IBD patient population in each country. For example, in developing countries where ulcerative colitis-like phenotypes of IBD are more common, the per capita health care costs are lower than in populations where Crohn's disease is more common, given the higher per capita costs of managing Crohn's disease. A further consideration is the fact that countries differ widely in their proportions of public and private health care coverage; however, both impose

limitations on expenditures, particularly for costly investigative procedures and advanced, targeted immunological therapies.

'Access' refers to the ability of a patient to obtain care in a timely fashion. In addition to service availability, Guilford *et al.* identify three classes of factors which can act as barriers to patients obtaining health care.[9] Personal barriers include factors unique to an individual that act as barriers even if a health care service is available.. First, a person living with disease has to perceive that they need care and then seek it out. Even then, fear or distrust of the medical system can be barriers to pursuing care; this distrust may be more prevalent in racialized or economically marginalized populations which have historically suffered abuses and injustices by the medical system.

Financial barriers are caused by the fact that patients are often expected to cover the costs for all or part of their health care; the decision to seek it out is impacted by their ability and willingness to pay these costs. In countries or regions without universal insurance, or where health care is not provided free of charge, the costs may render services inaccessible. Even in regions where insurance coverage is universal, the use of co-pays, deductibles, and selective coverage of high-cost services can erect a barrier to access, and one which is harder to overcome for individuals with fewer financial resources. Conversely, governments and/or insurers, as large purchasers of health care services, have the ability to use their market power to lower the price of health care services, such as biologics. In many countries, governments can use regulatory boards (such as the Patented Medicine Prices Review Board in Canada) to set maximum prices for medications, thereby improving the ability of patients to access these therapies.

Finally, organizational barriers include artificial constraints on the supply of services imposed by insurers and governments to slow the rate of consumption and thus lower their expenditures. This can appear in the form of limiting access to diagnostic testing, medical procedures, and expensive drugs. In IBD, it may take the form of requiring pre-authorization for access to high-cost biologics, requiring a referral to be seen by an IBD specialist, limiting the hours of endoscopy units, or by capitating physician payments.

### 2.1.3 Indirect Costs of Care

The indirect costs of care are those incurred by patients that impact their ability to contribute to society, as well as costs incurred in the process of seeking out care. Contributing to society most often takes the form of paid work but can also entail helping other people remain or become employed (e.g., through child-rearing or unpaid domestic work). The degree to which IBD impairs one's ability to generate public and personal capital defines disease-related disability, be it directly or indirectly.

Examples of indirect costs incurred by individuals with IBD are absenteeism, which includes loss of paid work due to sick days, short- and long-term disability, early retirement, premature death, leave for caregivers, and the inability to provide unpaid domestic help; and presenteeism, defined as reduced work productivity despite being present in the paid or domestic work environment, and impeded professional development. Indirect costs are typically calculated using the human capital approach,[10] which substitutes earnings as a proxy of direct economic activity and presumes that lost earnings due to disease-related disability represents the amount of economic activity lost to society.

The relationship between disease burden and the severity of disability depends on many variables; that is to say, two people with IBD of equivalent severity may experience vastly different levels of disability. IBD-related disability tends to increase in the presence of other medical comorbidities, mental health disorders, certain personality traits (decreased resilience, catastrophizing), as well as educational background, vocational training, a society's adaptability to different disabilities, and patient expectations and socioeconomic status.

To summarize, the total costs of IBD are determined by disease prevalence and severity, the availability and costs of health care services, and the severity of disease-related disability. The impact of any intervention, innovation, or other trend on the disease-related costs of IBD should be understood through this universal model.

## 2.2 What Are the Direct Health Care Costs of Inflammatory Bowel Diseases?

Patients diagnosed with IBD require long-term medical care, including frequent physician visits, multiple medical tests and medical management, hospitalizations, and surgeries. , As part of this commission, we searched the literature for representative direct and indirect cost studies from high-income countries (as defined by the World Bank) during the biological era (i.e., 1998 onwards, when infliximab was introduced in the US). Several factors exert a considerable influence on health care services (selection of tests, choice of medication, frequency of follow-up, among others) which, in turn, impact the data reported – and all of which affects the generalizability (external validity, applicability) of these studies' results to other settings and populations. This and the next section therefore only attempt summarize the available studies. The search strategy as well as the identified studies can be found in full detail in the Supplementary file and table (pp 1-4 and 9).

The costs associated with health care vary throughout patients' disease courses. Most studies have shown that total costs are much higher in the first year after a diagnosis than in subsequent years. Hospitalizations and diagnostic tests account for more than 50% of the costs during the first year; in subsequent years there is a steady increase in expenditure on biological agents, which account for approximately 80% of the costs in Crohn's diseaseand 50% in ulcerative colitis five years after diagnosis.[11]

The direct costs of IBD management have shifted substantially in recent years, primarily due to the emergence of biological therapy. Prior to the introduction of biologics, most direct costs were associated with IBD-related hospitalization, especially for those being admitted for surgery or for the management of irreversible complications of medically refractory IBD. For example, Odes *et al.* analysed health care costs in a Western European-Israeli population-based inception cohort of 1,321 patients who were followed for ten years from 1993 until 2004, i.e., essentially a pre-biologic era study.[12] Using physician-reported data, they determined the mean annual total direct costs were €1,871 per patient for IBD, €2,548 for Crohn's disease, and €1,524 for ulcerative colitis. Medical and surgical hospitalizations together accounted for 53%, and 5-aminosalicylic acid (5-ASA) formulations for as much as 25%, of the mean annual cost per IBD patient. 5-ASA accounted for 66% of the annual cost for medications in Crohn's disease, and 84% in ulcerative colitis. Anti-TNF agents were scarcely used in Europe and Israel during the study period, and their impact on costs was therefore minimal. However, country of origin was a significant determinant of cost, suggesting that widely different health care approaches to IBD prevailed.

In 1998, infliximab was introduced in the US for patients with Crohn's disease and it had an immediate impact on the direct costs of care. Kappelman *et al.* (2008) performed a retrospective cost analysis based on commercial insurance claims from administrative databases in 33 US states between 2003 and 2004.[13] The mean annual direct costs among 9,056 patients with Crohn's disease and 10,364 patients with ulcerative colitis amounted to $8,265 and $5,066 per patient, respectively. For Crohn's disease, 31% of costs were for medical and surgical hospitalizations, 33% for outpatient care, and 35% for medications; for ulcerative colitis, these proportions were 38%, 35%, and 27%, respectively. Anti-TNF and 5-ASA accounted for 44% and 15% of the costs of Crohn's disease, respectively; in ulcerative colitis, the proportions were 5% and 36%, respectively. The differences in costs between Europe and the US were likely due to differing patient populations and health care systems, and a greater use of biologics in the US.

Biologics have become the predominant driver of direct health care costs in the West. In recent years, therapeutic objectives have emphasized greater control over the disease, with the ultimate goal of achieving and maintaining complete mucosal healing to avoid progressive, irreversible bowel damage.[14] This new goal relies upon more frequent diagnostic tests (endoscopy, diagnostic imaging, and laboratory services), more specialist consultations, and more intensive (and expensive) targeted therapies. Furthermore, new management algorithms recommend introducing biological therapies earlier on in patients with aggressive disease phenotypes or those failing to respond to conventional therapies, while also promoting higher-dosage regimens.[15]

Several studies have observed a marked increase in the use of immunosuppressive and biological drugs, particularly among Crohn's disease patients. In IBD cohorts from around 2010, approximately 20% of Crohn's disease patients were receiving biological drugs one year after a diagnosis, and 30% were receiving them five years after a diagnosis.[16] In patients with ulcerative colitis, only about 10% of patients had been treated with biologics five years after a diagnosis.[17] However, in more recent cohorts approximately 30% of Crohn's diseaseand 10% of ulcerative colitis patients were being treated with biologics a year after diagnosis.[18–20] For example, in Manitoba, Canada, medication costs have increased tremendously during the last decade, from approximately 30% to 75% of total expenditures in Crohn's diseaseand from 20% to 60% in ulcerative colitis.[21] Anti-TNF agents account for over 90% of all medication costs in Crohn's diseaseand 80% in ulcerative colitis; they account for over 70% of the total health care costs in Crohn's diseaseand over 60% in ulcerative colitis.[21]

Despite the increased use of biological agents in IBD treatment, expenditure on hospitalizations and surgeries has been lowered only modestly, and the mean per capita costs spent on biologics in recent years is higher than what has been saved in hospitalizations per capita.[22,23] In fact, the direct costs of treating IBD have dramatically increased over the last decade. New biologics and small molecules are also expected to be approved in the coming years, which is likely to further increase the economic burden of IBD. However, it is possible that these drivers might be offset by the recent patent expirations for infliximab and adalimumab in much of the Western world, which has allowed for increased competition in the form of biosimilar agents and a reduction in prices.

### 2.2.5 Summary

Converting the costs from studies identified in the literature search (Supplementary File) in the period 2010 through 2017 into US dollars at the current exchange rates (September 12th, 2021), results in a mean annual direct cost of treating Crohn's disease of $12,294, while for ulcerative colitisit is $8,782. Our estimate of the direct cost of treating IBD patients is based on highly variable data, given the differences in the health care systems analysed, the time periods in which studies were performed, the selection of cohorts (age groups, disease duration, etc.), data abstraction methods, and study duration. Therefore, such a number should be interpretated with care. Furthermore, studies taking inflation and how this might impact on increasing costs over time into consideration are missing. Also, cost studies for biosimilars have not yet been reported.

However, the three most consistent findings from studies carried out in the biological era are: (1) treating Crohn's disease remains more expensive than treating ulcerative colitis; (2) biologics escalate treatment costs, and these are not offset by possible reductions in hospitalizations and other costs; and (3) direct costs in the US are far higher than in all other countries examined. Future studies will need to account for the decreasing cost of anti-TNF therapy following the widespread adoption of biosimilars.

## 2.3 What Are the Indirect Health Care Costs of Inflammatory Bowel Diseases?

Although indirect costs account for a major portion of total costs among patients with IBD, there are few studies addressing the topic (Supplementary File, pp. 5-8). This paucity of data can be ascribed to the difficulty of measuring indirect costs, as well as the lack of high-quality data sources. Most studies that assess the indirect impact of IBD focus on those aspects that are relatively easy to measure, such as the impact of IBD on employment and workplace productivity; lost wages; and societal spending to support people who are unable to attain financial independence due to disability, in the form of unemployment benefits, pensions, subsidized housing, etc. Unfortunately, the effects on educational achievement and any subsequent reduction in employment, costs for family members in attending appointments, or staying home to look after relatives with IBD are not captured.

The cost of productivity losses for both Crohn's diseaseand ulcerative colitis within the first five years of diagnosis account for up to 60% of the societal costs of IBD[24]. Several studies have shown that IBD patients are increasingly incurring higher costs for their health care, in the form of out-of-pocket expenses and workplace productivity losses[25–27]. Indirect costs are higher in patients with severe disease and comorbidities including psychological disorders. Crohn's disease and ulcerative colitis do not differ significantly in terms of the magnitude of indict costs in most studies.[26,28,29] the increasing use of biological agents in the 2000s vs. 2010s, the differences in indirect costs between IBD patients and controls have remained static.[25]

Most published studies evaluating the indirect costs of IBD focus on workplace attendance, with fewer commenting on presenteeism or other societal costs. However, IBD affects patients in many ways other than absenteeism and these are insufficiently described in the literature. A no less important fact are the differences between countries' social support systems, which can substantially alter the indirect costs for patients with IBD. Finally, very few of these studies are population-based or used nationwide cohorts, limiting the generalizability of their results.

### 2.3.5 Summary

Indirect costs have been only incompletely researched. Further studies are needed that address indirect costs other than lost work productivity, to more fully describe the substantial impact of IBD on patients. Nonetheless, the studies that are available suggest that indirect costs account for a substantial proportion of the total spent on patients with IBD, albeit with considerable variation between countries. Some of the differences between study results arise from diverse patient populations, distinct methodologies, and variations in the social support systems between countries. The most consistently identified drivers of indirect costs were active and more severe disease and comorbidities, including psychological disorders.

## 2.4. How Expensive Will IBD Be in the Future?

The cost of IBD in the future will be influenced by three main trends. First, the overall total costs will be affected by changes in the number of patients diagnosed with IBD. Second, mean and overall costs will be affected by changes in treatment patterns. Lastly, the price of the different interventions, and particularly the price of pharmaceuticals, will affect the overall costs.

### 2.4.1 Prevalence

Population-based epidemiological studies from North America and Europe have demonstrated the compounding prevalence of IBD over the past two decades.[2] Since 2000, prevalence increased by 3% and 4% per year in Canada and Scotland, respectively.[30,31] The prevalence of IBD was demonstrated to be ~0·5% of the general population in Canada, the US, and Scotland in 2010, is estimated to be ~0·75% in 2020, and is forecast to reach approximately 1% of the population by 2030.[32] Heterogeneity in the prevalence of IBD exists throughout the West; for example, the

prevalence in Portugal was only 0·1% in 2003, but has increased by ~5% per year, with the estimated prevalence having increased two-to-three-fold by 2019 and is forecast to be as high as 0·49% by 2030.[33] These data suggest the prevalence of IBD in the West could range between 0·5% and 1% over the next decade. Recent reviews of the literature also indicate that as the prevalence stabilizes in some countries, Asian countries that typically have had a lower prevalence are experiencing an upward trend. Altogether this points to a significant increase in the burden of IBD in the future. The increase in prevalence alone, if sustained at 3-4% a year, will lead to a doubling of health care costs between now and 2040.[34]

### 2.4.2 Trends in Treatments and Costs

In recent decades innovative new pharmaceuticals have led to changes in treatment for many patients with IBD. For instance, a study of patients with IBD based on individual-level patient data from the Medical Expenditure Panel Survey in the US concluded that the annual mean cost of treating an IBD patient nearly doubled between 1998 and 2015. Moreover, in the same period pharmaceutical expenses increased to become the largest cost driver, accounting for 44% of total expenditures.[35]

The cost of pharmaceuticals has increased the costs of treating patients, but could lower other costs. To the extent that new pharmaceuticals lead to improvements in the health-related quality of life for patients and delay the costs of disability, it will reduce the private and indirect public costs associated with IBD.

### 2.4.3 Trends in Prices of Treatments

The introduction of new pharmaceuticals will likely increase direct treatment costs initially, but as patents expire, the costs of pharmaceuticals will fall.[36] The introduction of new pharmaceuticals and biosimilars may also work to contain costs by increasing competition, but his effect seems to be stronger in Europe[37] than in the US.[38,39] In countries with a centralized system for buying and negotiating prices, this leads to large and immediate changes in costs. For instance, when the patent on adalimumab expired in Denmark in 2018, the authorities recommended the use of biosimilars. This resulted in a reported cost saving of 83%.[40]

Similar changes will occur in many countries in the future, but at the same time new, improved, and even more expensive treatments will also appear on the market. This will require the use of large-scale registries and improved, data-driven methods to quickly match patients with the best and most cost-effective pharmaceuticals.[41]

# 3. WHAT FACTORS DRIVE DIRECT COSTS IN IBD CARE?

## 3.1 COST-CONTROLLING MECHANISMS

Besides the increasing cost of pharmaceuticals (both biologics and small molecule drugs), IBD costs are also driven by the quality, reliability, and equitability of IBD care. To ensure the delivery of high-value care, as well as economic sustainability, we need continuous evaluations of existing and new therapies, standardization of care practices, and greater efficiency.

The most obvious way to lower spending on IBD would be to reduce the burden of IBD. Reducing the incidence of IBD could partially be accomplished by environmental risk factor modification strategies at the population level. However, in the absence of proven preventative strategies, the best way to reduce spending will most likely be to reduce the costs of treating IBD, such as by negotiating lower costs for medications.

Direct health care costs can be reduced either by lowering the price of a given health care service or by decreasing the rate at which that service is used (e.g., by restricting access to health care). These concepts are discussed below. Other ways of reducing costs include increasing non-physician IBD care (e.g., IBD nurse-led care or more extensive self-management plans) and eHealth, which reduces the cost per transaction. These are discussed in section 5.

While using price control regulations to lower the price of health care services may appeal to both providers and patients, there could be repercussions that lead to residual suffering on the part of patients. Lower prices for physician services may disincentivize providing care for IBD. In Ontario, Canada, the elimination of a premium paid to specialists for caring for IBD and other complex chronic diseases led to a drop in health care visits for those conditions.[42] This may have reduced costs without impairing quality of care if some visits were unnecessary. However, it might also have reduced access to specialists and negatively impacted quality of care. Similarly, lowering the price paid for drugs may discourage commercial innovators from investing in research and development; on the other hand, decreasing health care prices allows for health care to be delivered more equitably.

### 3.1.1 Controlling Costs by Lowering the Price per Transaction

Assuming a stable disease burden and steady demand for services, the cost of health care can be reduced either by imposing price controls or increasing competition among suppliers of those services. Price controls can be implemented by an external regulator, usually governmental, that imposes a maximum price for a drug or health care service, that is below the point where the price would be naturally set due to unencumbered market forces. The overarching purpose of a price control is to reduce costs for payers, allowing for the broader and more equitable distribution of the drug or health care service.

One of the major drivers of health care spending is the high price of innovator drugs. These prices are largely driven by the fact that most pharmaceutical innovators are granted a patent, during which time no competitors can sell an identical or similar drug. In order to improve access to innovative drugs, Canada, Australia, and most European countries have quasi-governmental boards that set a maximum price for a new drug. These boards set their prices by considering the needs of the population, as well as the prices of similar medications in that therapeutic space. Yet these panels must also take care not to set the price so low that companies are discouraged from continuing to invest in research and development. Additionally, many governments who are directly responsible for health care delivery will negotiate directly with pharmaceutical companies, demanding lower prices in exchange for access to a large pool of health care consumers.

Country-specific regulatory bodies generally impose limits on the duration of patents, after which time competitors can enter the marketplace. In Canada, the United States, the UK, and the EU, this

period lasts for 20 years. The true period of market exclusivity is much shorter, as many years may pass between the time a drug is patented and when it receives regulatory approval. Once the patent expires, competitors are allowed to develop biosimilar or generic versions of the drug. In the last five years, patents have expired for infliximab and adalimumab in much of the developed world; as a result, there are currently four infliximab biosimilars and six adalimumab biosimilars approved for use. The regulatory requirements for approval of biosimilar medications are far less stringent than for bio-originator molecules, allowing these medications to rapidly enter the marketplace. This increased competition has led to substantial decreases in the list prices for biological medications. For example, adalimumab biosimilars were first approved for use in Europe in 2018, and in some European countries prices have since dropped by more than 50%.[43]

In contrast, the US does not have a board that sets a maximum drug price and, by law, prohibits government insurers (national Medicare and state Medicaid programs) from negotiating lower prices with pharmaceutical companies. Additionally, the US court system has been much more favorable to plaintiffs who have sought to maintain exclusivity and prevent entry of competitors into the marketplace; this has resulted in US consumers paying significantly higher prices than the rest of the developed world for IBD therapeutics.

Table 2 lays out the great variation in costs of prescription drugs for IBD around the world. In individual countries there are differences in terms of the degree to which governments subsidize or provide financial coverage for medications. This high variability, especially for the costs of biologics in different places, underscores the potential lack of transparency in how pharmaceutical companies set their prices and, possibly, what other costs are added by governments or pharmacies.

### 3.1.2 Lowering Costs by Reducing the Number of Health Care Transactions

Health care providers can also throttle the ability of patients to access health care services in order to control costs. For people living with IBD, this can occur through several mechanisms such as requiring a patient or provider to demonstrate eligibility to access a drug or service, demanding patients provide payment of deductibles or co-pays, choosing not to provide or insure certain types of therapies or services, or limiting the availability of IBD care providers, facilities, or diagnostic testing, or cutting physician payments.

In some countries, capitation leads to payments to IBD specialists being reduced. As a health care visit is frequently the trigger for requesting more expensive health care services (e.g., initiating biologics, ordering diagnostic testing), limiting access to specialists invariably leads to lower downstream costs, though likely at the expense of worse patient outcomes.

Eligibility criteria are commonly used by insurers and service providers to reduce access to IBD drugs, especially biologics and other advanced therapies. For example, many insurers will have tiered access to IBD therapeutics, only providing coverage for higher-tier medications to patients who did not respond to or were intolerant of more expensive options; this may include a requirement for patients to have used less expensive drugs such as azathioprine or methotrexate before a biologic will be prescribed. Several countries, such as the United Kingdom and Denmark, have regulatory bodies that provide guidance about the prioritization of medicines based on their efficacy and cost assessments. However, this approach still carries the risk of exacerbating the disease by mandating inferior treatments prior to initiating biologics. Similarly, providers may require the use of a biosimilar anti-TNF before coverage will be provided for an originator biologic, or mandate switches from originator drugs to biosimilars.

### 3.1.2 Identifying High-Need, High-Cost Patients with IBD

Another way that providers can lower health care costs is through interventions targeting high-need, high-cost (HNHC) patients. As with other chronic diseases, a small percentage of IBD patients account for a disproportionately large share of total health care costs.[44] Compared with other IBD

patients, HNHC patients require far more care, particularly emergency department (ED) visits and hospitalizations.

A study from the US based on the 2013 Nationwide Readmission Database observed that a HNHC subset of IBD patients spent over 45 days in the hospital annually and accounted for 38% of total hospitalization costs (with median annual hospitalization costs ~$90,000 per patient) compared to a median of six days of hospitalization in the rest of the cohort.[45] Similarly, in the European Epi-IBD cohort, the 20% of patients with the highest costs during the first year after their diagnosis remained much more expensive throughout the five-year study than the remaining 80%.[11]

Patients at risk of progressing to HNHC remain difficult to identify with the models available.[46,47] Disease burden and drivers of health care usage are distinctly different in HNHC patients and are often amplified by behavioral health conditions and social risk factors, including psychiatric comorbidities, obesity, socioeconomic status and use of narcotics.[48] Some believe that the high expenditure on HNHC patients is preventable, or at least modifiable, through better disease control, coordination of care, preventative care and personalized interventions in the ambulatory care setting.[49–52] However, the majority of the data focus on readmissions following hospitalization or surgery and are based on electronic medical records and/or claims-based data that do not include the nonclinical risk factors necessary for building comprehensive risk management frameworks.

## 3.2 Appropriateness of Care and Improved Efficiency

As new options for treatment and prevention become available, it is important to demonstrate that any care being provided is appropriate, i.e., that its health benefits exceed its expected negative consequences. As resources are finite, health care providers generally seek to deliver services that provide the greatest reduction in disease burden at the lowest possible cost, a concept known as 'cost efficiency.'

### 3.2.1 Variability in Care and Standardizing Care to Facilitate Appropriate Health Care Delivery

Variability in care is a key barrier to achieving appropriate care in IBD.[53] Quality indicators can be used to objectively measure quality of care in chronic diseases and provide measurable standards for clinicians.[54,55] They are essential in identifying the magnitude of variability in care and monitoring improvement and, thus, for closing the gap between ideal and actual clinical performance.[56]

Often, clinicians may not realize that they are over-investigating patients, providing superfluous or harmful treatments, or applying high-cost treatments in an outdated or misinformed way. For example, the continued use of mesalazine in patients starting either immunomodulators or biologics is common but appears to be of little clinical benefit.[57,58] Additionally, the methods and frequency for monitoring IBD patients using blood and stool samples are not always evidence-based and sometimes unnecessary[59]. While there are limited data available to prove the economic consequences of inappropriate care in IBD, it is widely recognized that variability in care is a significant problem that raises direct and indirect costs.[60,61] Yet, very few electronic medical record systems document care in a way that gives clinicians, patients and/or providers the ability to monitor care quality in a way that provide mechanisms to enable visibility of unwarranted variation.[62]

Evidence-based clinical pathways are one strategy for standardizing care, improving appropriateness, and reducing variability in care, and thereby improve outcomes and reduce costs; but they are often complex, out of date, lack credibility, or poorly implemented.[63,64] Suboptimal adherence to international, evidence-based guidelines is an ongoing problem across various aspects of IBD care.[65–67] Clinician engagement, staying up-to-date with the research, and strategies to improve uptake are imperative if clinical pathways and guidelines are to improve the appropriateness of IBD care delivery. The best way of implementing international guidelines in clinical practice has

yet to be proven but minimizing variability by regularly updating clinical algorithms could represent one way to help standardize care.

### 3.2.2 Delivering Efficient Care

Efficiency is the allocation of available resources in a way that provides the best outcomes for the community. Inefficient care drives up costs. Vast sums are spent on health interventions that are irrelevant, redundant, or excessive; that provide few or no benefits; or that in some cases cause harm. In IBD, reactive, crisis-driven care has been correlated with higher costs than proactive (pre-emptive) care.[68] Patients in remission have the lowest costs of care and highest quality of life; patients responding to treatment have lower costs of care than patients with high disease activity who are not responding to treatment. Recent data suggest that the consequences of inefficient or low-value care are reflected in the indirect costs of lost productivity.[24,69,70] Thus, the total costs of care are more likely to be reduced by treatment that is effective and care that is efficient.[71,72]

### 3.2.3 Integrated Health Care Models

According to the WHO, integrated care models, encompassing a biopsychosocial approach to care, are the optimal way to standardize the management of chronic diseases such as IBD.[73] A multidisciplinary team approach to managing IBD is a central component of IBD care owing to the complexity of the disease, which is associated with extra-intestinal manifestations and complications needing specialist care.[74] While the members of the multidisciplinary team vary, accordingly to the complexity of care being delivered and the individual patient's needs, for the sake of efficiency it should include at least an IBD specialist-gastroenterologist, a surgeon, a radiologist, a pathologist, an IBD specialist nurse, a dietitian, and a pharmacist, with the option of specialists in psychology, dermatology, rheumatology, and ophthalmology.[75–77] A dedicated, multidisciplinary IBD service has been found to improve patients' psychosocial functioning and reduce hospitalizations and inpatient care, thereby increasing efficiency, even after accounting for the additional costs of the psychologist, social worker or dietitian etc. needed on the team.[78,79,80]

### 3.2.4 Participatory Care Models

Participatory health care models involve a collaboration between patient and physician and refer to a shift in which patients move from being merely passengers to co-pilots of their own health care. Participatory medicine promotes shared decision-making and facilitates patients' self-management of their disease. Digital health or eHealth tools incorporate a component of patient self-management whereby patients share information about their IBD with a program or health care team, from which patients can adjust their therapy based on algorithms.[81] This approach uses virtual clinics and has been found to reduce outpatient visits by up to 20%.[82] eHealth platforms, which facilitate participatory care models and support remote patient monitoring, have demonstrated improvements in disease activity, quality of life, quality of care delivery, and reductions in health care expenditure via reductions in outpatient visits, ED visits, and hospitalizations.[83] Constant Care in Denmark, and MyIBDCoach in the Netherlands, are web-based tools developed for remote IBD monitoring that have taken a participatory approach to integrated IBD care, focusing on disease activity, psychological wellbeing, preventative care, and the quality of care indicators. Compared to standard care, remote monitoring resulted in a significant decrease in outpatient visits and hospital admissions, improved quality of care, and significantly reduced the costs of care.[84–87] These early data suggest that participatory health care models have the potential to improve the appropriateness and efficiency of IBD care.

### 3.2.5 Population Health Management

Population health management (PHM) is an emerging concept within the field of IBD that can be defined as the coordination of care at a macroscopic level to improve outcomes and effectively manage both clinical and financial risk for patients.[88] PHM aims to improve quality of care, improve population health outcomes, and reduce health care costs by incorporating chronic care models, data sharing, shared decision-making, and risk profiling into population management goals.[44,88]

However, the extent to which PHM models can improve the appropriateness and efficiency of IBD care remains to be seen.

## 3.3 Inequality in Access to Care

Ethnicity and socioeconomic status (SES) are major contributors to health disparities, and unfavourable SES has been associated with poorer health outcomes and shorter life expectancy. It is therefore essential to account for these specific determinants when analysing a population's access to, and use of, health care resources. Access to care among socioeconomic minorities living with chronic diseases such as diabetes or rheumatoid arthritis has been studied for several decades and the disparity in access to care is a major reason for poorer health in those populations. In particular, a lack of long-term follow-up and higher rates of ED visits have been highlighted in disadvantaged social groups.[89]

In IBD, inequalities in access to care have been identified, as well. For example, diagnostic delay, defined as the time from first symptoms to diagnosis, may have an important impact on clinical management and prognosis. Median diagnostic delay varies between countries but is generally longer for Crohn's disease (median range: 4 to 9·5 months) than for ulcerative colitis (median range: 1 to 4 months).[90–93] Lower levels of education have also been associated with a longer diagnostic delay[93]. Once a diagnosis is established, patients may face additional delays in the management of their disease. A Canadian study demonstrated that lower-SES patients had a higher risk of delayed IBD-specific therapy after their diagnosis, as well as a higher risk of long-term non-use of an IBD-specific drug.[94] A subsequent study from Manitoba, Canada showed that people of lower SES had higher rates of hospitalization, longer hospital stays, and higher mortality, even though there was no apparent difference in their ability to access IBD-specific medications.[95] Variability was found in the use of steroids and immunomodulators, with fewer given to those of a non-white ethnicity or lower income.[96,97] Greater use of biologics was associated with higher SES, and access to biological treatments has been found to vary according to ethnicity. Two studies conducted in the US showed that African American patients were less likely to be prescribed infliximab.[98,99] Similar observations were found in Leicester, UK with a lower use of biological therapies among Asian patients than non-Asian, primarily Caucasian, patients.[100] However, access to drug treatments among ethnic minorities remains difficult to study, largely due to a lack of data, which usually relies on patient self-reporting rather than prescription databases. Self-reporting may confound any results due to non-adherence to therapy or providers' cost-reducing strategies for prescriptions.

No significant differences have been reported in accessing surgical interventions based on SES or ethnicity. However, a single study has found that a laparoscopic approach to colectomy was more often used in patients with private insurance than those with government-subsidized Medicaid insurance coverage (43% vs. 23%), suggesting that private insurance may increase access to less invasive surgical techniques, as well as specialized surgical consultations.[101] There could also be systemic cognitive bias driving surgical decision-making in certain clinical scenarios for IBD patients.

Rates of hospital admissions and ED visits have also varied according to insurance status. In the US, ED visits have been found to be 6.6 times more frequent in patients covered by Medicaid;[102] rates of ED visits were also higher for patients without health insurance.[103] These data suggest that low-income status is associated with an increased risk of not being able to access timely and effective care, which may impact long-term health, disease prognosis and, ultimately, costs. These findings are supported by a recent study demonstrating that IBD patients have more IBD medication prescriptions and fewer ED visits when followed at a US tertiary referral centre than at community hospitals, indicating possible differences between secondary health care systems and tertiary-oriented IBD subspecialty practices.[104] Higher rates of hospitalization have been found in African American IBD patients, with almost a threefold increase in patients covered by Medicaid, as compared to other types of insurance.[102] In a study from Manitoba, Canada people with IBD who

attended the ED and were not seen by a gastroenterologist were less likely to be seen by one during follow-up.[105] These ED visits incurred an extra cost of $1 million per year for a system that provides ED services for approximately 800,000 people.[106] This money could be allocated to a better care model, as outlined above. Finally, a Danish study identified greater difficulty for IBD patients to obtain life insurance compared to the general population, with the most common issue being a marked increase in premium weighting.[107]

These observations all point to a greater financial burden for lower-SES groups, and many questions about the influence of health insurance systems. We need a deeper, real-world understanding of how patients' lives, and the resources they access, may be shaped by gender, ethnicity, and SES, and how these drivers affect health outcomes (Figure 3). The study of other factors determining patients' access to care, such as travel distance to health services and out-of-pocket expenses, would also provide additional insight into the obstacles that patients face.

## 3.4 ADHERENCE

Patient adherence to treatment programs remains a critical element of successful disease management. The rate of non-adherence to medical treatment in IBD is around 50%, resulting in negative impacts on clinical outcome, morbidity and cost.[108] Adherence is important for prescribed treatments but also for disease monitoring. While it is recognised that chronic diseases are associated with suboptimal adherence, especially if the disease is in remission, a direct evaluation of outcomes has been more difficult to make. Not all physicians consider the relevance of adherence in their practice and even fewer use objective measures to quantify it, despite the widespread acknowledgment of its importance.[109]

Assessing adherence to oral medications with objective instruments is not easy and medication collection rates and self-reported questionnaires are the most frequently used methods. However, adherence to infusion-based biological therapies has been reported. In a retrospective study of 193 IBD patients, remission as measured by faecal calprotectin <100 ug/ml and CRP <5 mg/ml was strongly associated with adherence. Predictors of non-adherence were being male, shorter IBD duration and clinic non-attendance.[110] In a recent multicentre, cross-sectional study, subcutaneous administration was significantly associated with inadequate adherence to biologics (OR 4·8, 95%CI 1·57-14·66).[111] Elsewhere, in a claims database study of patients with IBD or rheumatoid arthritis, adherence was better for infusion-based biologics than for oral agents.[112]

A systematic review of risk factors for non-adherence to anti-TNF therapy identified being female, smoking, anxiety, and "moodiness."[113] In one tertiary centre study, a Crohn's disease diagnosis, insurance type, psychiatric history, smoking, prior use of biologics, and current use of narcotics were significantly associated with an increased risk of non-adherence;[114] adherence dropped to 42% when four of these risk factors were present. Adherence was significantly greater for more advanced therapies, with non-adherence occurring in 35·1% of 5-aminosalicylate users, 18·3% of thiopurine users and 7·4% of biological users. Patient beliefs about medication necessity and concerns about medication toxicity were the most important predictors of adherence.[115] A study from Spain of 234 patients treated with biologics found that 10% of them postponed hospital infusions and 5% delayed collection of subcutaneous vials at the hospital pharmacy.[116]

Interestingly, medication adherence in pregnancy differs among drug classes. In a Canadian study using administrative data, almost one-quarter of women with IBD who were previously adherent to medical therapy were not adherent during pregnancy. Women were more likely to be adherent to biologics than thiopurines and 5-aminosalicylates within their first trimester.[117] The perception that IBD medications may adversely affect child development during pregnancy is quite common and up to 22% of females believed that the risk of adverse events was greater than the risk of disease

relapse. There is an urgent need for pre-conception counselling to ensure women with IBD receive proper treatment during pregnancy.

High levels of patient activation – defined as having the knowledge, skills, and confidence to effectively manage one's own care – have been associated with improved outcomes in many chronic illnesses. Anxiety and depression have been implicated in decreased patient activation, while those with high activation were more likely to be in clinical remission at follow-up.[118] Structured interventions are vital, especially in high-risk patients. Preventative measures through telephone nurse counselling and the use of reminder systems, as well as the identification of patients at risk, could help to improve adherence to treatment.

The chronic and progressive course of IBD creates psychosocial discomfort for patients, so interventions are necessary at each step of treatment, beginning with their diagnosis and throughout long-term follow-up. For example, in Italy an agreement was reached in 2020 by a patients' association, the Catholic University, and the Istituto Superiore di Sanità to identify effective interventions for ensuring the highest degree of psychosocial assistance.[119] They determined that a multidisciplinary and coordinated team with integrated home-based assistance was the key to achieving the best quality of life. Patient engagement is essential in this process for ensuring adherence.

# 4: COST-EFFECTIVENESS IN INFLAMMATORY BOWEL DISEASES

## 4.1 LIMITATIONS OF RANDOMIZED CONTROLLED TRIALS

The randomized controlled trial (RCT) is considered to be the gold standard of biomedical research and there has been an exponential rise in published RCTs, and systematic reviews and meta analyses of RCTs, over the years.[120] RCTs are highly suited to comparing two or more similar treatments in a double-blinded setting, e.g., two different drugs or a placebo and a drug. At the same time, the past two decades have seen a shift in RCT endpoints used when studying IBD. This shift has been made possible thanks to the introduction of biological agents targeting specific cell types or cytokines. Approval of the first two anti-TNF agents, infliximab and adalimumab, relied on clinical response and clinical remission (based on the Crohn's Disease Activity Index (CDAI)), as clinical endpoints. Regulators have become more stringent in recent years, requiring endpoints that now include steroid-free remission and endoscopic improvement; but drug approval still largely depends on pure efficacy endpoints. Currently, regulators ask for co-primary endpoints including clinical remission and endoscopic response. Histological improvement in ulcerative colitis, and transmural healing for Crohn's disease, are now secondary endpoints and pave the way for new concepts of histo-endoscopic healing, mucosal healing, and disease clearance that combine clinical, endoscopic, and histological endpoints.

Although valid for drug development, there are a number of drawbacks to RCTs. First, they demand strict inclusion criteria, creating homogeneous groups to ensure high internal validity (the extent to which the observed results represent the truth in the population studied). However, the strictness of these criteria means the results cannot always be extrapolated to the general population (i.e., achieve external validity).[121] The general population can include paediatric, elderly, or pregnant patients, and those with or at increased risk of comorbidities such as infection, cancer, or cardiovascular disease, and certain ethnic groups.[122] Furthermore, there is variability in the background risk of infection worldwide, meaning that decisions around the cost-benefit of immunosuppression, in particular, will differ. In a cross-sectional study within the IBD Partners cohort reported by Johnson et al. (2020), only 7·6% of patients from a total of 14,747 patients with IBD reported RCT participation at any time.[123] The factors which were predictive of participation in a RCT were having Crohn's disease (more so than having ulcerative colitis), having more severe disease (including previous surgery, treatment with biologics), and being followed at an academic institution. In the case of IBD, RCTs will typically exclude specific subpopulations, such as isolated proctitis, patients failing several lines of biological therapies (who are considered to be too refractory), patients older than 75, those planning pregnancy, and patients with previous cancers and/or concomitant disorders. In a retrospective cohort study of adult IBD patients seen at a tertiary referral centre, only 31% of patients would have been eligible to participate in a RCT. The most frequent reasons for not being eligible were stricturing or penetrating Crohn's disease, high doses of steroids, and comorbidities or prior exposure to biologics.

The fact that many patients with moderate-to-severe IBD do not qualify for enrolment in RCTs raises questions about their external validity beyond the clinical trial populations.[121] At the same time, these challenges offer an opportunity, once a drug has been approved, for real-world studies in less restricted patient populations. Despite a sharp increase in the number of active RCTs, recruitment rates have decreased in recent years. These recruitment challenges prolong the drug approval process and put investigators at risk of so-called 'trial-fatigue.' The fall in recruitment rates could be linked to the greater administrative burden associated with RCTs, and/or a greater burden on patients (in the case of IBD, the mandatory ileo-colonoscopy at baseline and at the primary endpoint, as well as other examinations such as cardiac exams, ophthalmology and neurological work-ups, MRI, etc.) and stringent inclusion criteria. To improve recruitment rates, pharmaceutical companies are therefore expanding activities to new countries and continents such as Eastern Europe, South America, Russia, Asia, and India. Large community hospitals with the required staffing and setup for clinical trials are also a means for increasing recruitment rates.

Generally, most RCTs in IBD do not consider economic endpoints, although these would provide a useful additional dimension. The follow-up period in most RCTs is only long enough to measure the added cost of therapy in the short term but may not capture the full benefits of a new therapy over time. When including cost-effectiveness models in the design of a RCT, assumptions about the long-term efficacy and safety of a drug are needed, yet are often difficult to make. However, with more drugs being approved for IBD, incorporating cost-effectiveness analyses during RCTs may provide meaningful improvements in outcomes.

## 4.2 What Do We Know about the Cost-effectiveness of Treatments in Inflammatory Bowel Diseases?

Chronic diseases are the leading causes of illness, disability, death, and of growing health care spending in high-income countries. As a consequence, policy makers and health care professionals are becoming increasingly concerned about containing health care costs while improving the quality of patient care. Most of the available data focus on assessing cost-effectiveness, i.e., the extent to which the inputs used to produce a given output are minimized (productive efficiency). However, this does not indicate whether the right mix of health service outputs is being produced (allocative efficiency), or whether the right decisions are being made about how to use resources to maximize health and wellbeing over time (dynamic efficiency).[124] Several interrelated challenges must be overcome to build and analyse cost-effectiveness models of chronic diseases.[125] First, chronic diseases are much more prolonged than acute conditions and interventions to slow their progression may reduce complications years, or even decades, after the interventions (and their costs) occur.

Second, the duration of chronic diseases means that it can be costly and impractical to conduct clinical trials that directly test whether an intervention improves outcomes. When clinical trials are not feasible, simulation models are an attractive alternative for making predictions about likely cost-effectiveness. The need to develop simulation models leads to another major challenge: chronic diseases are usually complex, with progression depending on multiple risk factors that can produce widely varying complications. As a result, developing a cost-effectiveness model often focuses on disease progression. Clinical trials may provide evidence of an intervention's effects on intermediate outcomes, but it is then up to the disease progression model to simulate long-term outcomes.

Third, identifying the costs of complications in chronic disease modelling often receives inadequate attention compared to the time and effort devoted to modelling disease progression. Costs of averted complications cannot typically be estimated during a trial because these complications mostly begin to manifest years after the intervention.

Much uncertainty surrounds the relative cost-effectiveness of treatment options for IBD. Trials of the sufficient size and duration needed to answer the question of long-term cost-effectiveness have not been carried out and might never be. In addition, cost-effectiveness studies that do exist may not necessarily be transferable to other health care settings. The few studies we do have rely mostly on observational data of cost profiles before and after a specific intervention What follows is a summary of the available literature. A bibliographical search was performed in PubMed from inception up to February 2021 using the terms 'inflammatory bowel disease' or 'Crohn's disease' or 'ulcerative colitis' combined with 'cost-effectiveness' or 'cost-effective' and 'review' or 'meta-analysis.'

### 4.2.1 Immunosuppressive Treatment

*Methotrexate*

Mlcoch *et al*. evaluated the cost-effectiveness of parenteral methotrexate compared to standard care (i.e., high doses of oral corticosteroids followed by gradual tapering) for the treatment of mild-to-moderate Crohn's disease in the Czech Republic.[126] The authors developed a three-year Markov

model and over a three-year time-horizon methotrexate yielded an additional 0·111 quality-adjusted life-years (QALYs) at an additional cost of €513, with an incremental deterministic (probabilistic) cost-effectiveness ratio of €4,627 (€4,742)/QALY, far below the willingness-to-pay (WTP) threshold (≈ €47,000/QALY). The authors concluded that parenteral methotrexate proved to be cost-effective in patients with mild-to-moderate Crohn's disease.

*Thiopurines*
Vasudevan *et al*. assessed the cost-effectiveness of initial immunomodulators and anti-TNF agents for the treatment of Crohn's disease from a US third-party perspective, incorporating current treatment algorithms, optimization strategies, and the lower costs of biosimilars.[127] A one-year Markov model was developed to simulate the cost and QALYs of initial azathioprine, infliximab, and combination therapy for moderate-to-severe Crohn's disease. Initial azathioprine had the lowest cost and utility ($35,337 and 0·63 QALYs), while combination therapy was the costliest yet conferred the greatest health benefits ($57,638 and 0·67 QALYs). The authors concluded that in the era of biosimilars, initial azathioprine with escalation to infliximab appeared more cost-effective in the short term compared with infliximab or combination therapy, although initial combination therapy yields acceptable incremental cost-effectiveness ratios (ICERs) in the long term, with ongoing reductions in anti-TNF therapy costs, and will likely be the preferred treatment strategy in the future.

Vasudevan *et al*. performed a systematic review of economic analyses of strategies to optimise immunosuppressive therapy for IBD.[128] They then produced a qualitative synthesis of the studies identified, finding that both thiopurine methyltransferase (TPMT) testing before commencing thiopurines, and thiopurine metabolite testing for dose optimization, were cost-effective.

### 4.2.2 Treatment with Biologics
*Anti-TNF treatment*
In 2009, Bodger *et al*. assessed the cost-effectiveness of infliximab and adalimumab for Crohn's disease within the UK's NHS.[129] The model suggested acceptable ICERs for biological agents when considering a lifetime horizon with periods of up to four years of continuous therapy. In 2011, Bodger *et al*. reviewed the cost-effectiveness of treatments for IBD and showed that for Crohn's disease cost-utility models for anti-TNF drugs versus standard care consistently demonstrate incremental benefits, albeit it with an increased cost overall.[130] Pillai *et al*. performed a systematic review to assess the cost-effectiveness of treatment strategies for IBD.[131] They found that while biological agents helped to improve outcomes, they had high costs and were therefore not cost-effective, particularly when used as maintenance therapy. The authors noted that the cost-effectiveness of biological agents might improve as market prices fall with the introduction of biosimilars (their review was published in 2017).

Whether early biological therapy is more cost-effective than conventional therapy for Crohn's disease in adults is unclear due to a limited number of studies, insufficient data on endoscopic remission, and the heterogeneity of existing studies. Thomson *et al*. reviewed this topic and found that top-down therapy improved quality-adjusted life expectancy and reduced costs when compared to step-up therapy.[5,132] After one year the incremental cost-utility ratio was €92,440/QALY, while after four years it was €1,462/QALY. The authors conclude that early treatment with biologics does not have an obvious clinical benefit over conventional (step-up) therapy, despite some studies suggesting otherwise.

Vasudevan *et al*. performed a systematic review of economic analyses of strategies to optimise anti-TNFs for the treatment of IBD.[128] They then produced a qualitative synthesis of the studies identified, finding that multiple tailored approaches to treatment based on objective markers of disease activity or efficacy have been shown to be cost-effective in Crohn's disease, including following secondary loss of response to anti-TNF therapy for postoperative recurrence and in escalating treatment.

*Vedolizumab*
The current literature suggests that from a cost-effectiveness perspective vedolizumab might be a reasonable option for first- and second-line therapy for moderate-to-severe ulcerative colitis.[133] To date, there are no studies to suggest that vedolizumab would be the most cost-effective option for first-line therapy for moderate-to-severe Crohn's disease. However, studies suggest that vedolizumab could play a role later on in an individual's treatment course.[133] More studies are warranted to evaluate the comparative effectiveness of other biologics, as well as more recent advanced, targeted immunological therapies.

### 4.2.3 Summary
Several cost-effectiveness analyses, summarized in several systematic reviews and meta-analyses, have been performed for IBD (Table 3), most of which focus on anti-TNF treatments. Studies of varying design have produced a wide range of incremental cost-effectiveness estimates, which highlights the challenges and limitations of existing modelling techniques. Prices of originator drugs as well as the need for long-term treatment to maintain remission have led to most studies concluding that biologics are currently not cost-effective despite their proven efficacy. The cost-effectiveness of biological agents may improve as market prices fall and with the ongoing introduction of biosimilars. Our literature search also demonstrates that cost-effectiveness studies remain an area with room for improvement as studies evaluating the cost-effectiveness of drugs other than anti-TNFs (such as vedolizumab, ustekinumab, or tofacitinib), especially comparative studies with other drugs, are lacking despite some of them having been on the marked for several years.

Future research should identify optimal treatment strategies that reflect routine clinical practice and that incorporate indirect costs, new endpoints (such as endoscopic healing), and lifetime costs and benefits, all while taking into account the reduced cost of biosimilars. Additionally, as cost-effectiveness estimates may change in both directions with fluctuations in prices, cost-effectiveness studies are at risk of becoming outdated if not regularly maintained.

## 4.3 Are the Data Sources Available Adequate to Assess Cost-effectiveness?
Cost-effectiveness analyses are available on all advanced therapies; in some countries these studies are mandatory and also serve as the basis of reimbursement approval, while other countries have no such requirements. One of the most pressing limitations of these cost-utility analyses is that the drug and service costs are representative for the given country/region, but the outcomes and disease state transition probabilities used in Markov models are calculated from the landmark clinical trials. However, disease characteristics in real-world cohorts can significantly differ from that of RCTs, especially in Crohn's disease.[121] In some countries, prices for drugs and services can vary widely depending on patients' insurance plans (e.g., in the US). Thus, the local reimbursement environment is a significant confounder, and results from these studies cannot be directly extrapolated to different countries. Another limitation is that pharmacoeconomic analyses have validity only in the short term, since conclusions may change significantly with movements in drug/service reimbursement prices. Furthermore, the results are dependent on how the model is built (e.g., were indirect costs included and, if so, how detailed were the calculations?). For example, a very recent cost-effectiveness analysis from the UK concluded that although ferric carboxymaltose was the most effective iron supplementation therapy, its use was associated with a direct cost increase of 2,045 GBP per additional responder; however, indirect costs such as productivity losses were not calculated.[134] Similarly, a Swiss group[131] concluded in a systematic review based on 24 Crohn's disease and 25 ulcerative colitisstudies that maintenance biological therapies were not necessarily cost-effective, yet were associated with improved outcomes. In the future, cost-effectiveness studies need to be based on high-quality, real-world IBD cohorts to more accurately estimate disease outcomes[135]; ideally, better estimates of indirect costs would also be used.

Despite the abundance of cost-effectiveness reports based on extrapolations from landmark clinical trials, most clinical trials allow only a few patients representative of real-world patient populations to be included[121] and measure failure endpoints that do not resemble the real world. Furthermore, there is a significant imbalance in the geographical diversity of these data. Unsurprisingly, most data originate from North America and Western Europe, while far fewer data are available from other parts of the world (Table 3). Some data are available from Eastern Europe and Saudi Arabia, but largely missing from Asia, South America, Africa, or have been presented in abstract form only. Similarly, significant inequities in access to health care and biologics have been reported worldwide that have not been explained by epidemiological factors, drug prices or health care expenditures (e.g., in Eastern European countries). Cost-effectiveness, cost-utility and studies investigating access to advanced therapies could help alert decision-makers and result in more equitable reimbursement policies that ultimately lead to better access to biological therapies.

Another confounder in cost-effectiveness reports is cohort type. Patient cohorts from RCTs and referral IBD centres overestimate the probability of severe disease phenotypes and may report higher probabilities of outcomes (e.g., the need for advanced therapies, hospitalizations, surgeries, etc.). A more balanced analysis may be to base the models on RCT/referral centres and then re-run the analysis on high-quality, population-based inception cohort datasets. The two models are not mutually exclusive, but rather complementary. While the first represents the reality of referral centres, the second scenario is more appropriate for estimating the situation at a regional level. One example of such a study is the recent cost-effectiveness analysis of a European population-based inception cohort.[11]

The third input for cost-utility analyses, after costs and transition probabilities, is that of utilities. These measures of patients' perception of overall health status and preferences were traditionally derived from time-intensive processes (the standard gamble or the time trade-off), but in recent years have been derived from the EuroQol five-dimension questionnaire (EQ-5D) or the Short Form 6D (SF-6D).[136–138] Utilities are often derived prospectively in RCTs and are therefore subject to the same biases that have been pointed out with costs and transition probabilities — can these measures from highly selective patient populations be extrapolated to the real world?

Another potentially fruitful topic is the assessment of therapeutic sequencing, instead of assessing different therapies alone. Very few studies are available that report the comparative cost-effectiveness of early versus later therapies or sequencing of biological therapies.[139] For example, in 2017 a group led by Hungary evaluated the best sequence of biological therapies after the entry of biosimilars onto the market in nine different Western and Eastern European countries in luminal and fistulizing Crohn's disease based on economic considerations.[11] The conclusion was that biosimilars appeared to be the most cost-effective treatment, followed by using adalimumab and vedolizumab therapies, but there was a wide variation between the costs across the countries.

Most studies have concluded that biologics, despite their high costs, are cost-effective for the treatment of moderate-to-severe IBD. However, further research is needed from underrepresented regions. Furthermore, data based on outcomes from high-quality, real-world cohorts would likely better represent any cost-effectiveness that does exist. We need more research on estimating indirect costs, ideally based on real-world cohort studies (i.e., that include disability, absenteeism, presentism, etc). Future cost-effectiveness studies should look beyond simply assessing medical therapies and could investigate different treatment algorithms (e.g., early vs. late medication, medication sequencing, medical vs. surgical approaches for a specific scenario). In addition, a new wave of studies is approaching that will place greater emphasis on value-based care delivery instead of the more traditional cost analyses.[140]

## 4.4 Is Monitoring Disease Activity and Drug Concentrations Cost-effective in IBD?

### 4.4.1 Monitoring Strategies

Recently, the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE-II) initiative of the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) identified short, medium- and long-term targets for treatment based on a systematic review and expert consensus.[141] This work provides not only a framework for selecting targets, but also monitoring whether or not the targets are being met. Indeed, monitoring targets and responding appropriately are a vital part of the treat-to-target paradigm. STRIDE-II provides a framework for determining cost-effectiveness based on specific treatment targets and should be considered in future cost-effectiveness studies.

At present, endoscopic healing (and more recently histological healing for ulcerative colitis) is seen as the best treatment target for IBD patients, albeit with a degree of uncertainty around the definition of 'optimal' or 'deep' healing and a lack of data suggesting that changing therapy in patients with a partial response leads to improved outcomes. Repeated endoscopic monitoring is invasive, expensive and not without risk.[142] Therefore, non-invasive biomarkers that reflect endoscopic inflammation are attractive if they reliably reflect mucosal inflammation, are rapidly available to aid in decision-making, are cost-effective and reproducible.[143]

### 4.4.2 Short-term Target Monitoring

Although patients will appreciate the long-term benefits of mucosal healing such as fewer hospitalizations and surgeries and less disability, symptom relief is usually front of mind. This can be readily monitored using a range of patient-reported outcome measures (PROMs) such as the HBI, PRO-2, or CD-PRO for Crohn's disease and the SCCAI, PRO-2, or UC-PRO for ulcerative colitis.[144–148] Composite scores such as the CDAI and Truelove and Witts Severity Index combine clinical and laboratory data, while the Mayo score and others combine clinical and endoscopic data.[149–151] The benefits of symptom monitoring are the speed, low cost and alignment with patient priorities when they are experiencing active disease. However, there are significant limitations to solely monitoring and palliating symptoms for IBD patients. There is a poor correlation between symptoms and endoscopic inflammation, particularly in patients with small intestinal inflammation.[152] Even in the absence of symptoms, mucosal inflammation is associated with long-term complications, hospitalizations and surgeries.[153]

C-reactive protein (CRP), a serum marker that is cheap and readily available, has been shown to have a modest association with endoscopic inflammation, albeit more so in Crohn's disease than ulcerative colitis.[154] CRP has a higher specificity but lower sensitivity than faecal calprotectin (FC), suggesting that monitoring CRP early after treatment escalation gives a useful, if blunt, assessment of endoscopic inflammation.[155] Yet despite widespread clinical use, there are no cost-effectiveness studies to support the use of CRP for IBD monitoring.

### 4.4.3 Medium-term Target Monitoring

That FC is a more sensitive measure than CRP means that after a change in treatment FC will more accurately reflect mucosal healing. In the CALM study, symptom and biomarker (CRP and FC)-driven treatment escalation led to higher rates of endoscopic healing than symptom-driven escalation alone.[156] Post hoc analysis demonstrated that most of the treatment escalation in the biomarker symptom group was driven by high FC rather than CRP, suggesting that FC is a useful target and indicative of endoscopic inflammation.[141] Its cost-effectiveness was demonstrated in a UK analysis of the tight control arm using adalimumab escalation.[157] For children, resumption of normal growth is a key target and easily monitored biomarker of health.

### 4.4.4 Long-term Target Monitoring

Endoscopic healing, evaluated by ileocolonoscopy, is an important target in clinical trials, yet its role in a real-life setting among patients with a partial response remains uncertain. Ileocolonoscopy cannot be carried out repeatedly due to patient resistance and its high cost. Therefore, its judicious use in combination with PROMs and biomarkers is best, especially when important treatment decisions need to be made. Deep remission, comprising endoscopic and clinical remission, has also been shown to impede Crohn's diseaseprogression.[153] Monitoring quality of life and disability are also essential in the long-term. However, patient variables (e.g., mental health, comorbidities) and disease variables (e.g., fibrotic strictures, bile acid malabsorption) other than inflammation can affect both constructs and need to be investigated.

In addition to the targets endorsed in STRIDE II, monitoring other targets could also be useful and improve cost-effectiveness (Table 4). Cross-sectional imaging provides data on the intestine beyond the reach or view of endoscopy in Crohn's disease patients. However, both MRI and CT scanning are expensive and limited, with CT being the greatest source of diagnostic medical radiation. Intestinal ultrasound is a rapid and cost-effective monitoring tool in centres with the necessary equipment and expertise. In ulcerative colitispatients, there is additional benefit in monitoring histology over and above endoscopy and, where therapeutic options allow, escalating treatment to normalise histology should be considered (and is the subject of ongoing randomized studies, e.g., NCT04259138). In the future, PROM and inflammatory biomarker combinations, biomarker–TDM (therapeutic drug monitoring) combinations, or new biomarkers discovered through multi-'omics' profiling are likely to surpass the accuracy of FC and other single biomarkers.[158–162] However, currently the cost of multi-'omics' profiling is prohibitive, even if there were strong data to support its use.

### 4.4.5 Treatment Optimisation

Monitoring in IBD is useful to determine both disease activity as a therapeutic target and drug concentration as a determinant of dose adequacy and drug pharmacokinetics. Thiopurine drug monitoring has been used to confirm adherence and understand inter-individual differences in drug metabolism that could lead to therapeutic strategies for improving efficacy.[163] However, TDM can be used either reactively or proactively to optimise anti-TNF drug dose or ensure timely switching within or between classes of biologics. Reactive TDM refers to its use at the time of clinical manifestations, such as treatment failure or suspected toxicity. Proactive TDM refers to routine monitoring of drug concentrations at pre-defined time points, irrespective of whether the patient is in remission or has active disease. Anti-drug antibodies (ADAs) are a common cause of therapeutic failure and are measured as part of TDM, in addition to drug concentrations. Despite both the TAXIT (Trough Level Adapted Infliximab Treatment) and TAILORIX (Tailored treatment with infliximab for active Crohn's disease) studies failing to demonstrate a benefit to proactive TDM,[164] numerous retrospective studies have suggested that proactive TDM and measuring anti-drug antibody concentrations can guide decisions about anti-TNF withdrawal or restarting after a drug holiday.[165–172]

In 2017, a systematic review concluded that reactive TDM strategies lead to major cost savings in anti-TNF therapy (in both IBD and rheumatoid arthritis patients), with no negative impact on efficacy.[173] The modelling studies used have recently been reviewed by Yao *et al*. who found the overall quality to be moderate-to-high, although they did note the absence of productivity cost assessments.[139] The conclusion of both reviews was that TDM of infliximab was cost-effective. However, these studies are limited by the fact that the low TDM/antibody probabilities reported in real-world cohorts vary significantly; these models are based on soft data and have very wide confidence intervals.

The most recent cost-effectiveness analysis (published in 2021) — including RCTs, pharmacoeconomic and observational studies — concluded that reactive TDM of infliximab optimises dosing and reduces expenditure by over 50%, without affecting clinical outcomes.[169,170,174–

[178] It also concluded that proactive infliximab TDM may confer long-term clinical benefits, but is only modestly cost-effective.[179] Recent randomised Norwegian studies have addressed the proactive TDM-based approach to infliximab dosing across a range of inflammatory indications, including IBD. These studies showed that proactive TDM was no better at inducing clinical remission in patients newly prescribed infliximab. However, a proactive TDM approach was found to be significantly more effective than standard care during the maintenance phase of infliximab treatment.[180,181] No cost-effectiveness analysis was made in these studies.

The cost-effectiveness of anti-TNF TDM is difficult to prove at a societal level. There may be direct cost reductions where anti-TNF is discontinued due to lack of response despite high drug levels, or low drug levels with antibody formation.[182] However, the cost for newer biologics and small molecules for patients with failing anti-TNF drugs is high. Future studies of treatment decisions based on inflammatory biomarkers and drug concentrations are needed that measure both direct and indirect costs. Without such studies it is difficult to understand the benefits of monitoring targets as part of treatment. Further studies are needed to understand the cost-effectiveness of TDM for thiopurines and biologics other than infliximab (including adalimumab, vedolizumab, and ustekinumab) and whether its cost-effectiveness is altered by using biosimilars.[179]

# 5. How Can We Deliver Affordable IBD Care in High-Income Countries?

## 5.1 Cost-saving Measures

When choosing therapy for patients with IBD, some of the most important considerations are effectiveness, safety, patient preference and cost. With the advent of biological and oral small molecule therapies a further important consideration is route of administration. While these parameters are used to formulate therapeutic decisions, ultimately every health care provider is limited by the local availability of therapies, which is itself driven by costs.

Prior to the advent of biological drugs, thiopurines and methotrexate were the mainstay of immunomodulating therapies. Corticosteroids, which are inexpensive worldwide, have continued to be used to induce remission in moderate-to-severely ill patients and there is evidence that thiopurines and methotrexate are effective at maintaining remission.[183] Even though studies such as SONIC and SUCCESS have proven that an anti-TNF plus thiopurine is superior to a thiopurine alone in managing Crohn's disease and ulcerative colitis,[184,185] many patients respond well to thiopurines, which are considerably cheaper than biological therapy[186]. In industrialized countries a dichotomy has emerged whereby thiopurines continue to be a mainstay of IBD therapy in Europe and Australasia, but are increasingly considered only an adjunctive therapy in North America.[187]

The use of combination therapy with thiopurines or methotrexate increases the cost of biological therapy, but at least with anti-TNF therapy this is offset by improved outcomes that lead to enhanced health-related quality of life and a reduction in other expenditures, such as for hospitalizations and surgeries.[184,185] Determining the exact cost savings by choosing one therapy over another highly dependent on local costs. Surgeries are much less costly in Canada than in the US, for instance, while biological therapy may be similarly priced in both countries. Hence, anti-TNF therapy does not reduce direct costs even if it reduces the strain on health care resources[22]. If surgeries are less costly, then a well-timed surgery may be more cost-effective in select scenarios, such as Crohn's disease limited to a short segment of the terminal ileum[188]. In a Canadian population-based study, infliximab therapy was not found to reduce hospitalization and surgery rates in cases of Crohn's disease or UC. The authors speculate that the failure to demonstrate reductions was potentially related to misguided use of infliximab in patients with Crohn's disease and an underuse of infliximab in patients with UC.[189]

While biological therapies have been revolutionary in our management of IBD, they have driven costs up exponentially.[21,25,190,191] There are two main approaches that have emerged to mitigate these costs. The first has been the introduction of biosimilars. These compounds have proven to be comparably effective to their originator molecules.[192] The biosimilar industry has put downward pressure on the costs of biological therapies. In Canada, the ten provincial governments that oversee the health insurance provider programs have mandated initiating biological therapy with biosimilars rather than the originator compounds. Mandatory switching to biosimilars is now common in Europe as well. In some places a mandatory switch from an originator to a biosimilar compound for long-term users of biologics has been instituted.[193] With drugs of the same class being offered either subcutaneously or intravenously, there is some evidence that subcutaneous administration may be less expensive according to one analysis of direct/indirect costs that excluded acquisition costs.[194] However, adherence might fall with subcutaneous, rather than intravenous, therapies and the impact of non-adherence on costs has yet to be determined.

A second approach to reducing costs has been to de-escalate therapy when deep remission has been achieved, using regular patient monitoring for disease activity through serology, endoscopy, and radiology. While the precise timing of measuring drug levels and the optimal dosing of certain drugs continue to be debated, it is clear that drug level and antibody measurements can be useful

for guiding drug dosing and can improve cost-effectiveness.[139] For instance, a person in deep remission, that is to say with no symptoms and with a normal serum haemoglobin, normal CRP, normal serum albumin, and a normal ileocolonoscopy, who has been on weekly adalimumab for five years, might be de-escalated to therapy every other week. Recently, data from the Lengthening adalimumab dosing interval in quiescent Crohn's disease patients (LADI) study, reported that increasing adalimumab dosing interval from two to up to four weeks in quiescent Crohn's disease patients was non-inferior in terms of persistent flares (>8 weeks duration) and led to lower use of the drug.[195] However, clinical remission rates at the end of the study were lower in the control group continuing treatment every other week indicating that this approach might only be relevant in a subset of patients. Outright discontinuation of a biological therapy might also be considered, but current controlled trials assessing discontinuation have failed, partly because they withdrew treatment too early on in the course of therapy.[196–198] In terms of discontinuation of the immunomodulator when combination therapy is proving successful, a systematic review did not arrive at a firm conclusion as to the merit of this approach.[199]

Another potential source for cost-savings is the use of intestinal ultrasound for the diagnosis and monitoring of IBD.[200,201] Intestinal ultrasound has high accuracy, sensitivity, and specificity compared with other modalities, such as MR and CT, in both Crohn's disease and ulcerative colitispatients[202,203] and is non-invasive, unlike endoscopy. Intestinal ultrasound has been shown to reduce the need for additional endoscopy and MRI and, thereby, costs when used as a regular tool for disease monitoring[204].

## 5.2 Environmental Risk Factor Modification: Reducing Incidence and Disease Severity

Since the turn of the twenty-first century, the incidence of IBD has begun to stabilize, and in some regions fall, in the Western world. In contrast, newly industrialized countries in Asia, Africa and Latin America are observing rapidly rising incidence rates of IBD.[34] The primary driver of the changing incidence of IBD throughout the world are modifications of the environmental determinants of IBD.[205] Numerous studies have explored the impact of environmental risk factors on the risk of developing IBD. For example, smoking is associated with an increased risk of Crohn's disease, whereas quitting smoking is associated with a higher risk of ulcerative colitis. Early exposure to antibiotics increases the risk of developing IBD, whereas breastfeeding protects against IBD. Diet has a profound effect on IBD risk, with Western diets associated with refined sugars and highly processed food contributing to the onset of IBD. Consequently, environmental risk modification strategies at a population level, or targeting individuals at high risk of developing IBD (e.g., first-degree relatives), offer the potential to prevent IBD and reduce incidence over time.[8,206]

Environmental risk factor modification is a strategy to reduce the cost of IBD care for those with established disease.[207] Diet and lifestyle factors (e.g., smoking) are associated with worsening symptoms and disease course. For example, individuals who continue to smoke following a diagnosis of Crohn's diseaseare at higher risk of early surgical intervention and postoperative recurrence. In contrast, smoking cessation following the diagnosis of Crohn's diseaseis associated with improved disease course, including a reduced risk of flare-ups or of requiring escalation of medical or surgical management. A cost-effectiveness analysis demonstrated that a smoking cessation program targeting those with Crohn's diseasesaved millions of health care dollars within the first five years of patients quitting smoking, as well as significant downstream health savings from smoking-related complications such as cardiovascular disease and cancer.[208]

## 5.3 Dissemination, Implementation, and Quality Improvement for Increasing Care Reliability

### 5.3.1 American Models

In the United States, health care costs associated with IBD in 2016 were estimated to be $25·4 billion/year, a substantial portion of which originated in ED costs and hospitalizations.[209] However, much of this expenditure could be avoidable. It stands to reason that improving access, reliability, and quality of care through low-cost process changes may advance the triple aims of health care: improving patient experience and health outcomes while reducing per capita costs.

A 2014 retrospective chart review of seven paediatric IBD centres demonstrated that approximately 20% of ED visits were medically unnecessary and 50% were considered avoidable if the health system were more responsive and better coordinated.[210] In response to this opportunity, a number of initiatives have recently been established with the broad goal of optimizing outpatient IBD care in an effort to reduce unplanned emergency department visits and hospitalizations. The ImproveCareNow Paediatric IBD network was created to improve the reliability and quality of chronic illness care and its results over the last decade indicate sustained improvements in remission.[211]

In parallel, an adult IBD learning health system, IBD Qorus, a national quality improvement program in partnership with patients' associations, has been developed that emphasizes the patient-physician relationship. It has used a Breakthrough Series (BTS) Collaborative approach to quality improvement (QI) to enhance the delivery of outpatient IBD urgent care.[212] The initiative tested 19 ideas for change over 15 months at 24 centres across the US and observed modest decreases in ED use (18% to 14%) and hospitalization (14% to 11%). Based on a Markov decision model, participation in the urgent care intervention decreased costs by $2,949/year per patient when compared to the baseline.

Another recent innovation is the IBD Specialty Medical Home (SMH), pioneered by the University of Pittsburgh. In the SMH, coordinated care is provided by a multidisciplinary team comprising a social worker, dietitian, schedulers, nurse coordinators, and advanced practice providers, and it is led by a gastroenterologist and a psychiatrist. This model resulted in a 47·3% reduction in ED visits, a 35·9% reduction in hospitalizations and better quality of life.[50] Subsequently, Project Sonar has expanded this model to the private practice setting and incorporates 1) an EMR-embedded set of decision support tools based on published care pathways, 2) a risk assessment tool, 3) a technology-enhanced patient engagement platform, and 4) regular use of commercial claims data to analyse the impact of the program. Initial results from a single centre suggest reductions in unplanned hospitalizations and ED use, and the project is soon to be introduced at dozens of additional practices.[213]

### 5.3.2 British Model

In an effort to improve the overall quality, reliability and safety of care for IBD patients in the UK, a national audit, in addition to quality improvement initiatives, was begun in 2014 and is planned to run for 12 years.[214] The objectives of the programme are to assess the structure and organisation of care and the processes and outcomes of care delivery. It also aims to allow hospitals to assess their service delivery against national standards and to facilitate a process for improving the quality of care. Data are being captured on inpatient care, inpatient experiences, primary care services, the service structure, and biological therapies, and has evolved from retrospective to prospective data collection.

The results of the initial audit prompted the development of the national IBD Standards document in 2009, which was updated in 2013 and 2019.[215,216] Subsequent audit rounds enabled hospitals to see how their services compared with national standards and with other hospitals. This feedback helped individual hospitals improve key aspects of their service and the programme was able to guide quality improvement initiatives, including national-level plans, workshops with defined projects, and the

sharing of best practices. Improvements in quality of IBD care that were noted and measured by the national audit included a decrease in adult mortality during admission from 1·54% in 2008 to 0·75% in 2014, an increase in the number of hospitals with an IBD nurse (from 56% to 86%), an increase in the number of sites with a dedicated gastroenterology ward, a decrease in time from diagnosis to initial treatment with biologics, and a reduction in the frequency of surgery prior to biological therapy.

Rates of participation in the audit process increased from around 76% in the first audit round to more than 95% by the end of the process. How was this achieved? What were the levers? Each hospital had a 'lead clinician' to take responsibility and the Chief Executive of the hospital was kept informed of the process. The teams were engaged throughout the process with regular feedback, and involvement of the national charity and gastroenterology society ensured widespread dissemination of its results. The programme initially received funding from the Health Foundation, followed later by NHS funding of around £2 million over the 12-year project, equating to around £115 per patient in the audit. The initiative has been adopted by other countries such as the Netherlands, Australia, and New Zealand.

While further work is needed to refine and disseminate the interventions and determine whether the improvements in outcomes and cost savings are sustainable in the long-term, these early initiatives provide a proof of concept that using QI and implementation science can yield improved care at a lower cost.

## 5.4 PATIENT-CENTRED CARE IN IBD

### 5.4.1 Education and Empowerment

Education is of paramount importance for ensuring the optimal allocation of resources. This is true for both patients and physicians. The physician-patient relationship is integral to the decision-making process. Doctors should be trained to review evidence of treatment modalities and new techniques, and they should be aware of the cost of each treatment plan and alternative strategies. Knowledge of the cost-effectiveness of each treatment plan is essential for ensuring effective and affordable care. Patients should also recognize that adherence is one of the key factors in a treatment's success. Moreover, to ensure informed decision-making patients need access to both clinical and cost information about their treatment options. While the use of biologics has set new targets in disease management and has transformed IBD care, patients and physicians may have different hierarchies of needs. Patients must be educated about the merits and potential adverse effects of treatments, but also the importance of treatment monitoring and adherence. Physicians must also learn what their patients want and what their patients are prepared to do to achieve it. Treatments used inappropriately will be even less cost-effective. While patient education leads to patient empowerment, and patient empowerment and shared decision-making has gained popularity in clinical practice, the extent to which patients wish to be involved in selecting treatment varies greatly.[217]

### 5.4.2 Coordinated Care

An evidence-based care pathway can help to optimize care choices. Disease monitoring is crucial and has evolved with the growth of telemedicine during the COVID-19 pandemic. However, the positive effects of home-based care have been apparent since the early 2010s in patients with ulcerative colitis. In a randomised controlled trial in Denmark and Ireland, patients with ulcerative colitiswere randomised to web-based education and self-treatment or continuing with their usual care for 12 months. The number of acute and routine visits to the outpatient clinic was lower in the web-based group than in the control group, resulting in a saving of €189 per patient per year. Home-based care also empowers patients with ulcerative colitiswithout increasing their physical or mental health morbidity.[86,218] In one Dutch study, telemedicine resulted in lower mean annual costs of €547/patient (95% CI, €-1,029-2,143). This translated to an increased incremental cost-effectiveness over standard care in 83% of replications and an incremental net monetary benefit of €707/patient

(95% CI, €1,241-2,544).[84] In a Spanish study, a web-based platform showed promise as being more cost-effective than standard and telephone care.[219]

A separate study using electronic health screening showed equal efficacy in using scheduled interventions or on-demand monitoring in patients with ulcerative colitis.[220] Self-management with home-monitoring of disease activity has been shown to result in significantly faster remission compared to standard care.[220] Similarly, personalized, multidisciplinary care plans are necessary because of the chronic nature of IBD, the typically young age of the affected population, the complications and multiple interventions that occur, and the extraintestinal organ systems that can be affected. The in-house IBD mobile app developed by the Leuven group, with full integration within the electronic medical records, enabled continuous remote monitoring and allowed for the accurate detection of flare-ups.[220] Overall, telemedicine systems are safe and feasible for the management of IBD and are met with high acceptance from patients. Information and communication technologies can be used to enhance medication adherence, empowering patients to control their disease and optimize drugs during times of active disease, which can lead to fewer outpatient visits and less time away from school and work.

## 5.5 IBD NURSES

The care for IBD patients should ideally be provided by a dedicated, multidisciplinary team including physicians, nurses, dieticians, surgeons, psychologists, pathologists, and social workers. The role of the IBD nurse in access to education, advice, and support is central in this team. Specialized IBD nurses contribute to the care of IBD patients in many ways. Coenen *et al*. prospectively recorded all nurse-patient contacts in the first year after introducing an IBD nurse in their tertiary IBD practice and correlated more than 1,300 contacts with outcomes.[221] The IBD nurse provided counselling at the start of new therapy or during follow-up, provided information about the disease, helped with managing flare-ups, provided psychosocial support, and assisted with questions about side effects. Having an IBD nurse in place provided faster access to procedures and other departments for some patients. The most important finding was that the IBD nurse position resulted in a decrease in emergency room visits and unscheduled outpatient visits, hence reducing direct costs.[221,222] The value of IBD nurses as the first point of contact and counselling is obvious, although their cost-savings may also be associated with these contacts.

A nationwide study in Finland demonstrated the impact of an IBD nurse on the quality of care and on budget savings. Clinics with an IBD nurse reported fewer patient hospitalizations (4-9% vs. 11-19%, $p$ <0·001) and resulted in reallocating physicians' time.[223] In this way the estimated annual cost savings of having an IBD nurse may be significant and should be further mapped. A retrospective cohort study from Australia demonstrated the economic impact of implementing a nurse-led IBD advice-line and virtual clinic, which led to an annual net benefit of $11,663 AUD.[224] Furthermore, data from a district general hospital in the UK showed that a nurse-led telephone advice line was a cost-effective intervention by preventing unnecessary emergency or hospital visits, and appointments with general practitioners or consultants.[225]

It is becoming more apparent that including an IBD nurse in an IBD team is cost-effective.[226] So why then do not all IBD centres have IBD nurses? A survey among IBD nurses and nursing services across Canada showed large differences in training and diplomas (53·8% were diploma-prepared registered nurses, 35·3% Baccalaureate-prepared nurses, and 4·4% Master's-prepared nurses) and also large regional differences.[227] There might also be a maldistribution of the practice locations of IBD nurses; in the same survey almost half of all nurses were employed in Ontario, followed by 20% in the province of Alberta and 9% in British Columbia. Many nurses, although working with IBD patients, also held multiple roles and responsibilities, and provided a variety of services. Further studies evaluating IBD nurses' scope of practice, regional differences in the provision of IBD nursing

care, and barriers and enablers of access to IBD nurse positions within and between countries are required.

## 5.6 Future Directions

Measures to reduce the costs of IBD care are summarised in Table 5 as well as suggestions as how to implement these measures. Increases in health care costs must be evaluated against improved disease control and reductions in indirect costs. Evaluations should be systematically aligned between countries and regions (e.g., using systems such as NICE or ICER). Detailed analysis of the current epidemiology and the likely effects of changing IBD management on disease course and socioeconomic outcomes is essential; this will become even more imperative in the era of precision medicine, where complex biotechnologies will require expensive analyses, highly skilled personnel, and drug development for what may sometimes be relatively small patient groups.

New therapies, treatment algorithms, and care models will continue to be developed; thus, establishing overarching systems for data interoperability, registries, and big data approaches for continuous assessment of the costs and cost-effectiveness of care is essential. There is a need for global collaboration and international IBD consortia-driven efforts that focus on establishing and consolidating epidemiological research platforms (e.g., combining comprehensive clinical data with data from national health and social security registries) to estimate short- and long-term socioeconomic outcomes, including health care usage by patients and society, and evaluate incidence, with carefully curated health-care utilization and cost data.

Developing models that facilitate economic evaluations in targeted treatment as well as comparative effectiveness studies of the different medical and surgical interventions to help inform value-based decision-making could ultimately lead to more sustainable and more effective treatments, as well as cost-effective clinical trials. This requires efforts to facilitate IBD data interoperability, to help perform comparative effectiveness research studies for more accurate comparisons of outcomes.

Precision medicine is currently being applied to IBD via treat-to-target goals, therapeutic drug monitoring, stratification via serologic response to antimicrobial antigens, and genetic data (TPMT and NUDT15).[4] However, development of increasingly sophisticated decision support tools to make phenotypic and prognostic recommendations based on patient findings (genetic profile, protein expression at the tissue level, and microbial signature) is currently underway and represents an important component of precision medicine.[228] Precision medicine is also being applied to the delivery of targeted therapies based on complex and proactive dashboard modelling that includes pharmacogenomic and other patient-specific factors—instead of trial and error—to reduce exposure to ineffective medicine and avoid toxicity, as well as toobtain response and remission faster, reducing compications and costs.[229] Although expected to drive significant costs, there are efficiencies and economies in attaining precision that could potentially offset such costs in the future.

Demonstrating that costs are also driven by the quality of IBD care allows for an opportunity to further define potential low-value patterns of practice and standardize quality indicators to ensure more appropriate, better-value care. For a sustainable IBD health care infrastructure, high-income countries have a responsibility to assess the efficiency of health care delivery in IBD and to use this evidence to support the highest-value interventions and care. Transnational non-profit organizations (such as the European Crohn's and Colitis Organisation and International Organization for the Study of Inflammatory Bowel Disease), in collaboration with patient organizations, should take responsibility for establishing optimal strategies for implementing international guidelines and supporting country-specific implementation of the most efficient care models.

This should be done by assessing the barriers to implementing guidelines, developing more strategies to improve the appropriateness and efficiency of care, performing studies that evaluate

novel models of care (such as value-based health care, including integrated health care and participatory health care models), and finding new approaches to improving quality through the education and training of clinicians, patients, and policy makers. In this way, aligning IBD expertise can more uniformly and systematically bring about a harmonized globalization of IBD care, where the cost-effectiveness of new approaches can be evaluated based on consensus.

While this Commission has focused on the situation in high-income countries, confronting the challenge of increasing costs of IBD care will also be of great importance in the low- and middle-income regions of Asia, Africa, and South America. In these regions, the incidence and prevalence rates of IBD are set to increase rapidly in the coming years, which they will need to tackle despite having severely limited resources. This necessitates high-quality economic evaluations, service delivery interventions, and evidence supporting the optimal configuration of services in high-income countries, from which most of our current data originate.

# 6. SUMMARY

Estimating the true costs of IBD within a region, or comparing costs between regions/countries, can be difficult due to the vast heterogeneity of health care systems and a lack of transparency in how prices for medications and services are set across the world. However, the increasing financial burden of IBD on health care systems has been reported from practically all regions of the industrialized world.

Cost increases have primarily been driven by the introduction of new and costly treatments, together with ever more intensive and expensive disease monitoring and treatment paradigms that use more frequent testing and that start treatment with costly agents earlier and more often. But other important factors at a societal and structural level also contribute to rising costs, including inequality in access to care and a lack of means to optimize patient involvement and adherence. Continuous education and subspecialisation of the gastroenterologist is paramount for the cost-effective diagnosis, treatment and follow-up of IBD patients.

As the prevalence of IBD continues to increase, so will its costs. In view of the inevitable increase in spending on IBD management, some key questions remain: 1) Will the anticipated increase in spending on novel therapies be offset by improved patient outcomes and reductions in disease burden? 2) What effect will the emergence of more stringent treatment targets and earlier, more aggressive treatment have on per-capita spending on IBD? 3) What cost savings can we expect from the greater uptake of cheaper alternatives such as biosimilars and the adoption of digital health tools?

This Commission has identified some key areas in which progress is needed at the national and international levels. First, the responsibility of countering increasing costs lies, in part, with the treating physicians and with the research community. Both need accurate cost-effectiveness studies of current treatments and strategies, which are currently lacking. They should urgently be undertaken to serve as platforms for assessing the efficiency of health care delivery and for informing providers of where costs arise.

Other initiatives to battle increasing costs must come from governments or payer/health care systems. The aim should be to improve access to care, and its reliability and quality, including supporting implementation of new models that make use of value-based care concepts. These solutions should ideally be informed by large data sets from patients in real-world care settings, with feedback loops for continuous quality improvement. In these ways, we believe that high-value and affordable IBD care can be provided without detracting from treatment quality, and that the management tools, evidence, and methods used to achieve this care can be made available to affect a transformation across all developed countries.

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# 8. FIGURE LEGENDS

Figure 1. Drivers of direct and indirect costs of inflammatory bowel disease.

Figure 2. Annual distribution of costs for patients with Crohn's disease and ulcerative colitis in a European inception cohort (from Burisch *et al*.[11]).

Figure 3. Inequality in access to inflammatory bowel disease care.

**Title**

The Costs of Inflammatory Bowel Diseases in High-Income Settings

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All other authors declare no conflicts of interest.

**Authors' contributions**

Part 1, summary and abstract: JB, MZ and PM wrote and edited the text. Part 2: SO (odes@bgu.ac.il) led the section. GK, DD, DG, HOM, MW and HAS contributed to the concept development, writing, and editing of the text. Part 3: PDC (ppdecruz@gmail.com) led the section. LT, VP, VA, KTP, KK, MH, ZK and MC contributed to the concept development, writing, and editing of the text. Part 4: Severine Vermeire (severine.vermeire@uzleuven.be) led the section. EVL, PLL, JPG, WB, BM, and RG contributed to the concept development, writing, and editing of the text. Part 5: CB (Charles.Bernstein@umanitoba.ca) led the section. MK, AH, MP, JA, SN and RF contributed to the concept development, writing, and editing of the text. JB and PM oversaw the coordination and writing of the report.

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## ABSTRACT

The cost of caring for patients with inflammatory bowel diseases (IBD) continues to increase worldwide. The cause is not only a steady increase in the prevalence of Crohn's disease ~~(CD)~~ and ulcerative colitis ~~(UC)~~ in both developed and newly industrialized countries, but also the chronic nature of the diseases, the need for long-term, often expensive treatments, the use of more intensive disease monitoring strategies, and the impact of the diseases on economic productivity. This report draws together a wide range of expertise to discuss the current costs of IBD care, the drivers of increasing costs, and how to deliver affordable care for IBD in the future. The key conclusions are that (i) increases in health care costs must be evaluated against improved disease management and reductions in indirect costs, and (ii) that overarching systems for data interoperability, registries, and big data approaches must be established for continuous assessment of effectiveness, costs, and the cost-effectiveness of care. International collaborations should be sought out in order to evaluate novel models of care (such as value-based health care, including integrated health care and participatory health care models), as well as to improve the education and training of clinicians, patients, and policymakers.



~~**Keywords**~~

~~Crohn's disease; ulcerative colitis; health care costs; health care utilization; direct costs; indirect costs~~

# 1. INTRODUCTION

Crohn's disease ~~(CD)~~ and ulcerative colitis ~~(UC)~~, together known as inflammatory bowel diseases (IBD), affect approximately seven million people globally.[1] A recent report from the Global Burden of Disease Study described a surge in IBD incidence in emerging countries and a steady prevalence in developed countries. As such, the number of patients living with IBD will continue to grow, with a prevalence rate forecast to approach 1% within the next ten years in some regions.[2] Due to IBD's incurability and unpredictable disease course, lifelong monitoring and treatment are often required to prevent disease progression and complications that impair patients' quality of life and ability to work.[3]

The continuing rise in IBD prevalence and aging populations worldwide will inevitably lead to an increasing use of health care resources by patients with IBD. In parallel with these trends, continuing innovations in IBD therapeutics, diagnostics, and preventatives are creating more options for reducing the disease burden. The increasing availability of biological agents and small molecules marks the beginning of a new era in the management of IBD, as early, aggressive treatment and treat-to-target become more common.[4,5] These trends will all place a burden on health care systems and require that we identify modifiable cost drivers and develop strategies for delivering equitable and affordable IBD care for all patients.

Meanwhile, wide variations in social support systems and rules for reimbursement across countries hinder efforts to estimate the global cost burden of IBD. For instance, the US ranks higher in health care spending per capita than other Western countries and this is partially explained by a lack of central regulation of drug prices, something that is certainly affecting US data for IBD care.[6] The lack of transparency in drug pricing and the paucity of data about indirect costs, such as productivity losses and work disability among IBD patients, further distort our estimations of costs and cost-effectiveness.

The *Lancet Gastroenterology & Hepatology* Commission, consisting of a diverse faculty of health care professionals with expertise in the field of IBD and health economists, was formed to deliver an extensive summary of the literature and discuss key topics on the costs and cost-effectiveness of treating IBD currently, and how it is likely to look in the future. Furthermore, we offer suggestions for how to deliver more affordable IBD care. The report's focus is on high-income countries in Europe, North America, Australia and New Zealand, and Asia. While the burden, and hence the costs, of IBD will increase significantly in low- and middle-income countries in the future as the incidence of IBD increases,[2] important differences between these countries in their social, health care, and economic structures means they are best discussed separately.

# 2. How Expensive Is IBD Care Now and How Expensive Will it Be in the Future?

## 2.1 A Framework for Understanding IBD-related Costs

The total cost of a chronic disease like IBD can be separated into direct costs (those incurred as a result of providing health care specifically targeting symptoms, signs, and sequelae) and indirect costs (those incurred by patients not directly related to the receipt of health care, and the impact that IBD and its sequelae have on economic productivity). The total cost of IBD can be understood as an interplay between four factors:
(1) overall disease burden;
(2) treatment and monitoring of IBD and related complications; (3)
access to, and utilization of, IBD-specific medical care; and (4)
impact of the disease on patients' ability to contribute economically.

### 2.1.1 Disease Burden

The concept of burden refers to the negative effects that living with a disease has on a person's state of well-being, physical health, and health-related quality of life. The disease burden across a population is a function of the prevalence of the disease and its severity among ~~sufferers~~those living with the disease. Disease burden is the main driver of both direct and indirect costs, in that it prompts health care-seeking behaviour (which is responsible for the direct costs) and to the extent to which it causes disability, impairment, or death, which limits ~~the sufferer's~~the patients ability to contribute to society (its indirect costs).

Currently, in the industrialized West, there is a compounding prevalence of IBD, whereby the number of people living with it is steadily increasing due to the nature of IBD as a chronic disease in which incidence greatly surpasses mortality.[7] The prevalence of IBD is anticipated to continue to rise throughout the world, even in countries where IBD has been uncommon until recently.[2] The prevalence of IBD can be lowered either by reducing the incidence of IBD through identifying and eliminating etiological factors, or by shortening disease duration by finding a cure or delaying the onset of disease. Similarly, the burden of IBD can be ameliorated through developing and implementing effective therapies that reduce disease severity or prevent complications and comorbidities, e.g., mental health issues such as anxiety and depression, and by improving methods for earlier detection and close monitoring for complications.[8] Table 1 offers a summary of these demographic, behavioural, and disease-related characteristics.

### 2.1.2 Direct Costs of Care

Defined broadly, the direct costs of care are the amount of money spent by individual patients and health care systems on services. The monetary costs of these services vary considerably depending on the country or region. This variability in direct costs between different countries is the result of several factors. The wealth of a country, and the resources it allocates to support the health of its citizens, affects the types of services that can be provided and the extent to which they are accessed by patients. The costs of developing and maintaining the infrastructure for delivering health care also varies considerably; this includes, but is not limited to, the costs of educating practitioners and support staff; the costs of developing facilities, medical equipment, and drugs; and the profits and wages paid to individuals and corporations for continued care and innovation.

In addition, governments and insurers differ in the extent to which they regulate the health care market through capping drug prices or reimbursing physicians, which further affects the costs of care. The demand for health care services is also partially determined by the demographics and disease behaviour in the IBD patient population in each country. For example, in developing countries where ~~UC~~ulcerative colitis-like phenotypes of IBD are more common, the per capita health care costs are lower than in populations where Crohn's disease~~CD~~ is more common, given the

higher per capita costs of managing ~~CD~~Crohn's disease. A further consideration is the fact that countries differ widely in their proportions of public and private health care coverage; however, both impose limitations on expenditures, particularly for costly investigative procedures and advanced, targeted immunological therapies.

'Access' refers to the ability of a patient to obtain care in a timely fashion. In addition to service availability, Guilford *et al.* identify three classes of factors which can act as barriers to patients obtaining health care.~~:~~[9]

~~a. P~~Personal barriers include factors unique to an individual that act as barriers ~~; E~~even if a health care service is available~~, there may be factors unique to an individual that act as barriers~~. First, a person living with disease has to perceive that they need care and then seek it out. Even then, fear or distrust of the medical system can be barriers to pursuing care; this distrust may be more prevalent in racialized or economically marginalized populations which have historically suffered abuses and injustices by the medical system.

~~b. ~~Financial barriers are caused by the fact that ~~; P~~patients are often expected to cover the costs for all or part of their health care; the decision to seek it out is impacted by their ability and willingness to pay these costs. In countries or regions without universal insurance, or where health care is not provided free of charge, the costs may render services inaccessible. Even in regions where insurance coverage is universal, the use of co-pays, deductibles, and selective coverage of high-cost services can erect a barrier to access, and one which is harder to overcome for individuals with fewer financial resources. Conversely, governments and/or insurers, as large purchasers of health care services, have the ability to use their market power to lower the price of health care services, such as biologics. In many countries, governments can use regulatory boards (such as the Patented Medicine Prices Review Board in Canada) to set maximum prices for medications, thereby improving the ability of patients to access these therapies.

~~c. ~~Finally, ~~Organizational~~ organizational barriers include artificial constraints on the supply of services imposed by ~~; ~~insurers and governments ~~sometimes impose artificial constraints on the supply of services in order ~~to slow the rate of consumption and thus lower their expenditures. This can appear in the form of limiting access to diagnostic testing, medical procedures, and expensive drugs. In IBD, it may take the form of requiring pre-authorization for access to high-cost biologics, requiring a referral to be seen by an IBD specialist, limiting the hours of endoscopy units, or by capitating physician payments.

**2.1.3 Indirect Costs of Care**

The indirect costs of care are those incurred by patients that impact their ability to contribute to society, as well as costs incurred in the process of seeking out care. Contributing to society most often takes the form of paid ~~work, but~~work but can also entail helping other people remain or become employed (e.g., through child-rearing or unpaid domestic work). The degree to which IBD impairs one's ability to generate public and personal capital defines disease-related disability, be it directly or indirectly.

Examples of indirect costs incurred by individuals with IBD are absenteeism, which includes loss of paid work due to sick days, short- and long-term disability, early retirement, premature death, leave for caregivers, and the inability to provide unpaid domestic help; and presenteeism, defined as reduced work productivity despite being present in the paid or domestic work environment, and impeded professional development. Indirect costs are typically calculated using the human capital approach,[10] which substitutes earnings as a proxy of direct economic activity and presumes that lost earnings due to disease-related disability represents the amount of economic activity lost to society.

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The relationship between disease burden and the severity of disability depends on many variables; that is to say, two people with IBD of equivalent severity may experience vastly different levels of disability. IBD-related disability tends to increase in the presence of other medical comorbidities, mental health disorders, certain personality traits (decreased resilience, catastrophizing), as well as educational background, vocational training, a society's adaptability to different disabilities, and patient expectations and socioeconomic status.

To summarize, the total costs of IBD are determined by disease prevalence and severity, the availability and costs of health care services, and the severity of disease-related disability. The impact of any intervention, innovation, or other trend on the disease-related costs of IBD should be understood through this universal model.

## 2.2 What Are the Direct Health Care Costs of Inflammatory Bowel Diseases?

Patients diagnosed with IBD require long-term medical care, including frequent physician visits, multiple medical tests and medical management, hospitalizations, and surgeries. ~~The costs associated with such resources vary throughout patients' disease courses, .~~ As part of this commission, we searched the literature for representative direct and indirect cost studies from high-income countries (as defined by the World Bank) during the biological era (i.e., 1998 onwards, when infliximab was introduced in the US). Several factors exert a considerable influence on health care services (selection of tests, choice of medication, frequency of follow-up, among others) which, in turn, impact the data reported – and all of which affects the generalizability (external validity, applicability) of these studies' results to other settings and populations. This and the next section therefore only attempt summarize the available studies. The search strategy as well as the identified studies can be found in full detail in the Supplementary file and table (pp 1-4 and 9).
~~Most studies have shown that total costs are much higher in the first year after a diagnosis than in subsequent years. Hospitalizations and diagnostic tests account for more than 50% of the costs during the first year; in subsequent years there is a steady increase in expenditure on biological agents, which account for approximately 80% of the costs in CD and 50% in UC five years after diagnosis.[11]~~

The costs associated with health care vary throughout patients' disease courses. Most studies have shown that total costs are much higher in the first year after a diagnosis than in subsequent years. Hospitalizations and diagnostic tests account for more than 50% of the costs during the first year; in subsequent years there is a steady increase in expenditure on biological agents, which account for approximately 80% of the costs in Crohn's diseaseand 50% in ulcerative colitis five years after diagnosis.[11]

The direct costs of IBD management have shifted substantially in recent years, primarily due to the emergence of biological therapy. Prior to the introduction of biologics, most direct costs were associated with IBD-related hospitalization, especially for those being admitted for surgery or for the management of irreversible complications of medically refractory IBD. For example, Odes *et al.* ~~(2006)~~ analysed health care costs in a Western European-Israeli population-based inception cohort of 1,321 patients who were followed for ten years from 1993 until 2004, i.e., essentially a pre-biologic era study.[12] Using physician-reported data, they determined the mean annual total direct costs were €1,871 per patient for IBD, €2,548 for ~~CD~~Crohn's disease, and €1,524 for ~~UC~~ulcerative colitis. Medical and surgical hospitalizations together accounted for 53%, and 5-aminosalicylic acid (5-ASA) formulations for as much as 25%, of the mean annual cost per IBD patient. 5-ASA accounted for 66% of the annual cost for medications in Crohn's disease~~CD~~, and 84% in ulcerative colitis~~UC~~. Anti-TNF agents were scarcely used in Europe and Israel during the study period, and their impact on costs was therefore minimal. However, country of origin was a significant determinant of cost, suggesting that widely different health care approaches to IBD prevailed.

In 1998, infliximab was introduced in the US for patients with Crohn's disease~~CD~~ and it had an immediate impact on the direct costs of care. Kappelman *et al.* (2008) performed a retrospective cost analysis based on commercial insurance claims from administrative databases in 33 US states between 2003 and 2004.[13] The mean annual direct costs among 9,056 patients with Crohn's disease~~CD~~ and 10,364 patients with ulcerative colitis~~UC~~ amounted to $8,265 and $5,066 per patient, respectively. For Crohn's disease~~CD~~, 31% of costs were for medical and surgical hospitalizations, 33% for outpatient care, and 35% for medications; for ulcerative colitis~~UC~~, these proportions were 38%, 35%, and 27%, respectively. Anti-TNF and 5-ASA accounted for 44% and 15% of the costs of Crohn's disease~~CD~~, respectively; in ulcerative colitis~~UC~~, the proportions were 5% and 36%, respectively. The differences in costs between Europe and the US were likely due to differing patient populations and health care systems, and a greater use of biologics in the US.

Biologics have become the predominant driver of direct health care costs in the West. In recent years, therapeutic objectives have emphasized greater control over the disease, with the ultimate goal of achieving and maintaining complete mucosal healing to avoid progressive, irreversible bowel damage.[14] This new goal relies upon more frequent diagnostic tests (endoscopy, diagnostic imaging, and laboratory services), more specialist consultations, and more intensive (and expensive) targeted therapies. Furthermore, new management algorithms recommend introducing biological therapies earlier on in patients with aggressive disease phenotypes or those failing to respond to conventional therapies, while also promoting higher-dosage regimens.[15]

Several studies have observed a marked increase in the use of immunosuppressive and biological drugs, particularly among ~~CD~~Crohn's disease patients. In IBD cohorts from around 2010, approximately 20% of Crohn's disease~~CD~~ patients were receiving biological drugs one year after a diagnosis, and 30% were receiving them five years after a diagnosis.[16] In patients with ulcerative colitis~~UC~~, only about 10% of patients had been treated with biologics five years after a diagnosis.[17] However, in more recent cohorts approximately 30% of Crohn's disease~~CD~~ and 10% of ulcerative colitis~~UC~~ patients were being treated with biologics a year after diagnosis.[18–20] For example, in Manitoba, Canada, ~~M~~medication costs have increased tremendously during the last decade, from approximately 30% to 75% of total expenditures in Crohn's disease~~CD~~ and from 20% to 60% in ulcerative colitis.~~UC~~[21]. Anti-TNF agents account for over 90% of all medication costs in Crohn's disease~~CD~~ and 80% in ulcerative colitis~~UC~~; they account for over 70% of the total health care costs in Crohn's disease~~CD~~ and over 60% in ulcerative colitis~~UC~~.[21]

Despite the increased use of biological agents in IBD treatment, expenditure on hospitalizations and surgeries has been lowered only modestly, and the mean per capita costs spent on biologics in recent years is higher than what has been saved in hospitalizations per capita.[22,23] In fact, the direct costs of treating IBD have dramatically increased over the last decade. New biologics and small molecules are also expected to be approved in the coming years, which is likely to further increase the economic burden of IBD. However, it is possible that these drivers might be offset by the recent patent expirations for infliximab and adalimumab in much of the Western world, which has allowed for increased competition in the form of biosimilar agents and a reduction in prices.

~~What follows is a review of representative direct cost studies from high-income countries (as defined by the World Bank). Articles in English were accessed on PubMed and Google Scholar. Studies selected for inclusion needed to be carried out in high-income countries during the biological era (i.e., 1998 onwards, when infliximab was introduced in the US), be based on defined populations or national patient registries or administrative (claims) databases, report data for cost per patient (prevalent or incident), and include direct and/or indirect costs. In countries where only single-hospital or multiple-hospital studies were reported, studies were included only if they met all other~~

criteria. The search criteria for identifying studies were: 'cost,' 'direct cost,' 'indirect cost,' 'inflammatory bowel disease,' 'Crohn's disease,' 'ulcerative colitis,' 'indeterminate colitis,' and 'inflammatory bowel disease unclassified.' Only full-length articles were reviewed; abstracts and conference reports were disregarded. Articles that reported total costs per disease, but not costs per patient, were excluded. As described in sections 2.2.5 and 2.3.5, no attempt was made to average out the cost data or synthesize the findings since the studies' methodologies were so different. Table 2 summarizes, as best we can, the pertinent results of these studies. As alluded to already, several factors exert a considerable influence on health care services (selection of tests, choice of medication, frequency of follow up, among others) which, in turn, impact the data reported – and all of which affects the generalizability (external validity, applicability) of these studies' results to other settings and populations.

**2.2.1 Europe**

There have been several European, population-based cohort studies of the direct costs of IBD care. Burisch *et al.* (2015) reported on first-year cost data for 1,367 newly diagnosed patients (710 UC, 509 CD, 148 IBDU), who were recruited beginning in 2010 from 20 European countries and Israel.[24] All costs were calculated using the Danish Health Cost Register. The mean annual direct health care cost for CD patients was calculated as €5,942, for UC it was €2,753, and for IBDU it was €2,898. In CD, standard treatment accounted for 15% of expenditure (5-ASA 5%), biologics for 20%, investigations for 31%, and surgery for 34%. In UC, standard treatment accounted for 30% of costs (5-ASA 27%), biologics for 8%, investigations for 45%, and surgery for 17%. The percentage of patients treated with biologics rose steadily during the years of follow-up, particularly in CD. The percentage of CD patients requiring surgery also increased during this period. Disease phenotype was found to be a cost-driver: younger patients were more expensive to treat, as were CD patients classified as B2 and B3, as well as UC patients with more extensive disease. Costs for IBD patients were higher in Western European countries than in Eastern Europe, particularly for biological medications.

The same authors published a five-year follow-up study in 2020 in which the costs per individual country were used and the disease diagnoses were reclassified as needed.[11] The cohort comprised 1,289 IBD patients: 1,073 (83%) from Western Europe and 216 (17%) from Eastern Europe. The mean annual cost per IBD patient was €2,609 (median €446). For CD, the mean annual cost was €3,542 (median €717), for UC it was €2,088 (median €408), and for IBDU it was €1,609 (median €415). Costs were highest in the first year after diagnosis, and then declined significantly during follow-up. Hospitalizations and investigations accounted for over 50% of costs during the first year, but in subsequent years there was a steady increase in expenditure on biologics, which accounted for 73% of costs in CD, and 48% in UC, in the fifth year after diagnosis. The mean annual cost for biologics in all IBD patients was €866; for CD it was €1,782, for UC it was €286, and for IBDU it was €521. However, most patients were not treated with biologics. Overall, biological therapy accounted for 33% of all costs, hospitalizations for 25%, investigations for 22%, surgery for 9%, and standard medications for 8%. In the first year after diagnosis, costs were driven by hospitalizations and investigations (amounting to more than 50% of total costs). In the fifth year, costs were driven by biological treatment (73% of the total costs in CD, 48% in UC). The mean annual cost of biologics in Western Europe was twice that in Eastern Europe. Higher costs were associated with diagnosis of CD, biological treatment, first year of diagnosis, current smoking in CD, previous smoking in UC, disease severity B3 in CD, and extent E2 and E3 in UC. (A description of the cost structures in the participating countries is given in Supplementary Table 1 of Burisch *et al.* 2020.)

Khalili *et al.* reported a cost analysis of data abstracted from the Swedish National Patient Register of prevalent IBD cases. In patients aged 18–64 years, the mean annual cost per CD patient was $10,094, of which biologics accounted for $4,495 (45%), standard medications for $1,335 (13%), outpatient visits for $1,926 (19%), and hospitalizations for $2,338 (23%).[25] In UC, the total mean

annual cost was $5,924; biologics accounted for 25% of this figure. Hospitalization charges were higher in older subjects; however, it was not stated whether these charges included treatment for comorbidities. In both the prevalent and incident cohorts, 15% of CD patients and 9% of UC patients accounted for 50% of the annual total cost.

Lo *et al.* retrieved data from the Danish National Patient Registry for 213 CD and 300 UC patients in Copenhagen between 2003–2016.[26] The mean annual direct cost per CD patient for hospitalization was €6,600, surgery was €4,100, biologics was €700, standard medication was €736, and investigations were €290. For UC, the corresponding costs were €4,700, €2,900, €300, €120, and €535, respectively. Vadstrup *et al.* (2020) reported on a much larger Danish cohort, stratified by year of diagnosis, between 2003–2015.[27] Hospitalization was the chief cost-driver in the first year in both CD and UC, and outpatient charges were the greatest driver in the fifth year. Medication costs remained low, possibly indicating a limited use of biologics.

Van der Valk *et al.* (2014) reported cost data in the Dutch physician-generated COIN study.[28] The total annual cost per patient was found to be lower in UC than CD. Costs for biologics and hospitalizations accounted for 64% and 19%, respectively, of the total cost in CD. By comparison, in UC biologics accounted for 19%, and hospitalizations for 14%, of the total cost. In CD, medication costs were driven by anti-TNF medications (64% of the total cost, with 23% of patients treated with anti-TNF). In UC, medication costs were driven by anti-TNF and 5-ASA (54% of the total cost, with 4% of patients treated with anti-TNF and 64% treated with 5-ASA). Predictors of high health care costs in CD included current flare-ups and penetrating disease, and in UC the predictors were current flare-ups and current ileostomy.

Aldeguer and Sicras-Mainar (2016) in Spain reported on 285 adult UC patients for the period 2002–2012.[29] The mean direct annual cost per UC patient was €1,754, of which medications accounted for 28% (biologics were not mentioned). By contrast, Pillai *et al.* (2019) in Switzerland found the total annual cost for CD to be €9,504 and for UC to be €5,704, with medications accounting for 70% and 68% of these costs, respectively.[30] Benedini *et al.* (2012) in Italy reported an annual total cost of direct care in CD of €18,838, with medications accounting for 50% of this figure.[31]

### 2.2.2 Australia

Two studies were reported from Melbourne. Niewiadomski *et al.* (2015), in a prospective study between 2007 and 2013, reported a mean annual cost per CD patient of $10,477 AUD, and for UC of $6,292 AUD.[32] Predictors of high costs during the first year of CD were perianal disease, L2–L3, and B2–B3; for UC, the predictors were disease extent E2–E3 and a CRP greater than ten. High-cost outliers with CD (11% of patients) or UC (10%) accounted for 42% and 36%, respectively, of total costs. Jackson *et al.* (2017) performed a retrospective tertiary centre cost analysis for one year, ending March 2015.[33] The annual median total cost for CD was $15,648 AUD, while for UC it was $5,017 AUD. Cost drivers were active disease and hospitalization. Outpatient services costs were higher for CD than for UC.

### 2.2.3 Asia

In Asia, access to drugs and the types of approved and reimbursed drugs vary between countries. For instance, in Japan all prices are fixed by the government. Since the Ministry of Health, Labour and Welfare in Japan reimburses all the costs of IBD care, including high-cost drugs such as biologics, neither patients nor hospitals bear the costs of care. In China, infliximab is not included in the social security policy and patients have to self-finance the cost, and adalimumab is currently regarded as having only off-label use for CD. In India, for patients who are below the poverty line, all government hospitals provide free medical therapies, including biologics, whereas other patients have to self-finance their drugs.

Kim *et al.* (2019) analysed data from a South Korean patient claims database between 2005–2015, when the CD patient population increased from 4,340 to 12,251, and UC from 10,701 to 23,811.[34] The mean annual direct health care cost of CD increased in this period from $1,178 to $3,192. For UC the direct costs increased from $413 to $798. The annual rate of biologic usage escalated from 39·8% to 93·1% in CD, and from 0·4% to 84·5% in UC. In 2015, anti-TNF therapies accounted for 69% of the total cost in CD, and 49% in UC. Treatment with anti-TNF was the strongest predictor of high costs among both UC and CD patients. Other predictors of higher costs were young age at onset, hospitalization, and surgery.

Lee *et al.* (2020) also showed that the cost of IBD in South Korea is driven by biological medications. In the period 2010–2012, the total direct cost in CD was $3,658 in the first year, $2,109 in the second year, and $2,120 in the third year.[35] The costs of biologics for those same years were $774 (20% of the first-year total cost), $1,052 (50%), and $1,274 (60%), respectively. In UC, the corresponding total annual costs were $1,758, $1,185, and $1,117, respectively; biologics accounted for $108 (6%), $215 (18%), and $282 (25%) of these total costs, respectively.

A study in Hong Kong found that hospitalizations and 5-ASA usage accounted for 56% of the total direct costs in the first two years after a new IBD diagnosis.[36] Direct costs were higher in the first year. Surgery and low haemoglobin on presentation were associated with higher costs.

### 2.2.4 North America

*United States*

Using the PharMetrics commercial insurance claims database, Kappelman *et al.* (2008) determined the mean annual cost for prevalent patients with IBD for the years 2003 and 2004 in the US.[13] The mean annual patient cost for CD was $8,265, and for UC it was $5,066. The most expensive item in the breakdown for CD was medications ($2,919), while in UC it was outpatient services ($1,768). Younger age (under 20 years) was associated with higher costs in both diseases. In CD, biologics accounted for 11% of the total cost, but in UC it was less than 2%. However, this study analysed data gathered prior to widespread use of biologics for the treatment of UC. In a secondary analysis, Kappelman *et al.* (2011) showed that patients with CD had more medical and surgical hospitalizations than patients with UC.[37] They also found that females and younger patients had more hospitalizations.

In an analysis of eleven US health insurance plans, Park *et al.* (2015) extracted data from a large, administrative database of 5,090 patients with CD.[38] For the entire cohort, the mean annual cost per patient was $18,637; for patients under the age of 18 it was $22,796, while for patients older than 18 it was $18,095. High-cost (Pareto sub-group, 28%) and low-cost (72%) patients had costs of $45,602 and $8,153, respectively; 20% of patients accounted for 80% of the mean annual cost. Biologics accounted for 30% of total yearly outlay, non-biologics 16%, and hospitalizations 23%. A subsequent report by Park *et al.* (2020) described costs for 23,720 CD and 29,062 UC patients with either commercial insurance or Medicare Advantage coverage and listed in the Optum Research Database.[39] Extrapolating from data shown in graphical form, the mean annual cost per IBD patient was determined to be $22,000 in 2008 and $30,000 in 2016. For CD, the mean annual cost in the first year was $30,000, rising to $38,000 by year 10; for UC, the corresponding costs were $25,000 and $15,000, respectively. Strong drivers of cost were being younger than 18 (where the cost was 1·4 times higher) and use of biologics (2·4 times higher). The rise in costs for CD, compared with the decrease of costs for UC, was attributed to the more widespread use of biological medications among CD patients.

Working with the Optum Research Health database, Cohen *et al.* (2015) showed that the direct health care costs in UC patients varied with the severity of the disease, with moderate-severe patients costing $22,874 per year versus $15,378 for a mixed total cohort.[40] Pilon *et al.* (2020) estimated the total cost per UC patient to be $18,198 per year.[41]

~~Dielemann *et al.* (2020) estimated annual health care spending in the US between 1996 and 2016 based on datasets that together covered 87% of all health-care spending during that period. After adjusting for changes in inflation, population size, and age groups, health care spending for IBD was estimated to have increased at an annualized rate of 5.9% and spending in 2016 was estimated to be $25.3 billion (95%CI 22.3-28.7). Generally, health conditions with the greatest changes in spending, such as rheumatoid arthritis and IBD, were also those that saw the introduction of specialty drug treatments, including biologics, during the period.[42]~~

~~*Canada*~~

~~Bernstein *et al.* (2012) used the University of Manitoba IBD Epidemiological Database to analyse cost by age, and found that the annual costs for CD were highest in patients younger than 18 years, at $4,174 CAD, followed by age groups 19–64 years at $3,875, and 65 years and older at $589.[23] The corresponding costs for UC were $3,364, $2,715 and $920, respectively. Targownik *et al.* (2019), using the same database, showed that in the period 2005–2015 the mean direct cost per CD patient increased from $4,640 to $10,747 CAD, and from $2,194 to $5,065 CAD for UC patients.[22] The main driver of these increases was the more widespread use and earlier adoption of anti-TNF therapy over time. While the mean annual cost for hospitalizations decreased for CD patients, it increased for UC patients. Higher per capita costs were also associated with being younger than 25 years and being male. These and other Canadian studies of direct costs were reviewed by Kuenzig *et al.* (2019), who found substantial variation (two-fold or more) among the provinces of Manitoba, Alberta, and Quebec.[43] Treating newly diagnosed CD or UC was 68% and 100% more expensive, respectively, than treating patients four years after a diagnosis. IBD patients receiving infliximab were always more expensive to treat than in the years prior to their receiving infliximab.[22] Biologics were used by 14·2% of CD and 4·1% of UC patients and were significant drivers of medication costs in all provinces. Overall, the direct health care cost of IBD in Canada in 2018 was estimated to be $1·28 billion annually, or roughly $4,731 CAD per person with IBD.[43]~~

**2.2.5 Summary**

Converting the costs from studies identified in the literature search (Supplementary File) in the period 2010 through 2017 into US dollars at the current exchange rates (September 12th, 2021), results in a mean annual direct cost of treating Crohn's disease of $12,294, while for ulcerative colitisit is $8,782. Our estimate of the direct cost of treating IBD patients is based on highly variable data, given the differences in the health care systems analysed, the time periods in which studies were performed, the selection of cohorts (age groups, disease duration, etc.), data abstraction methods, and study duration. Therefore, such a number should be interpretated with care. Furthermore, studies taking inflation and ~~its~~ this might impact on increasing costs over time into consideration are missing. Also, cost studies for biosimilars have not yet been reported.

However, the three most consistent findings from studies carried out in the biological era are: (1) treating Crohn's disease ~~CD~~ remains more expensive than treating ulcerative colitis~~UC~~; (2) biologics escalate treatment costs and these are not offset by possible reductions in hospitalizations and other costs; and (3) direct costs in the US are far higher than in all other countries examined. ~~Converting the costs from studies performed in the period 2010 through 2017 into US dollars at the current exchange rates (September 12th, 2021), results in a mean annual direct cost of treating CD of $12,294, while for UC it is $8,782.~~ Future studies will need to account for the decreasing cost of anti-TNF therapy following the widespread adoption of biosimilars.

## 2.3 What Are the Indirect Health Care Costs of Inflammatory Bowel Diseases?

Although indirect costs account for a major portion of total costs among patients with IBD, there are few studies addressing the topic (Supplementary ~~Table 2~~File, pp. 5-8). This paucity of data can be ascribed to the difficulty of measuring indirect costs, as well as the lack of high-quality data sources. Most studies that assess the indirect impact of IBD focus on those aspects that are relatively easy to measure, such as the impact of IBD on employment and workplace productivity; lost wages; and societal spending to support people who are unable to attain financial independence due to disability, in the form of unemployment benefits, pensions, subsidized housing, etc. Unfortunately, the effects on educational achievement and any subsequent reduction in employment, costs for family members in attending appointments, or staying home to look after relatives with IBD are not captured.

The cost of productivity losses for both Crohn's disease~~CD~~ and ulcerative colitis ~~UC~~ within the first five years of diagnosis account for up to 60% of the societal costs of IBD[24]. Several studies have shown that IBD patients are increasingly incurring higher costs for their health care, in the form of out-of-pocket expenses and workplace productivity losses[25–27]. Indirect costs are higher in patients with severe disease and comorbidities including psychological disorders. Crohn's disease and ulcerative colitis do not differ significantly in terms of the magnitude of indict costs in most studies.[26,28,29]~~Despite~~ the increasing use of biological agents in the 2000s vs. 2010s, the differences in indirect costs between IBD patients and controls have remained static.[25]~~.~~

Most published studies evaluating the indirect costs of IBD focus on workplace attendance, with fewer commenting on presenteeism or other societal costs. However, IBD affects patients in many ways other than absenteeism and these are insufficiently described in the literature. A no less important fact are the differences between countries' social support systems, which can substantially alter the indirect costs for patients with IBD. Finally, very few of these studies are population-based or used nationwide cohorts, limiting the generalizability of their results.

### ~~2.3.1 Europe~~

~~A study from Sweden by Khalili *et al.* (2020) used nationwide patient registries to analyse two cohorts: an incident cohort (2010–2013) and a prevalent cohort (2014), with a follow-up of one year.[25] The authors calculated costs resulting from lost productivity, including sick leave and disability pension. The mean cost per patient-year for total productivity losses was higher for CD than for UC, both in the incident (CD, $12,102; UC, $8,852) and prevalent cohorts (CD, $12,717; UC, $8,209). Patients with incident CD had higher mean costs for sick leave and lower costs for disability pension than prevalent patients (sick leave, $5,858 vs. $3,900; disability pension, $6,243 vs. $8,816). The respective incident versus prevalent costs for UC patients were sick leave, $4,073 vs. $3,118; disability pension, $4,778 vs. $5,091. In the prevalent cohort, the incremental increase in costs related to lost productivity compared to the respective general population was $6,771 for CD and $2,491 for UC. Productivity losses in the prevalent cohort accounted for the majority of the total (direct and indirect) health-related indirect cost (56% for CD, 59% for UC).~~

~~Two studies of population based Danish cohorts have been reported. Lo *et al.* (2019) recruited incident patients with IBD diagnosed prospectively between 2003 and 2004 in the Copenhagen area, with follow-up continuing until 2013/2014.[26] The median annual total indirect cost per patient was €2,700 in CD and €2,500 in UC. Data for the total indirect costs included paid sick leave (€1,100 in CD and €1,100 in UC), social security benefits (€1,900 in CD and €1,500 in UC), and loss of revenue from income tax (€700 in CD and €800 in UC). During follow-up, it was determined that the total health care cost (direct plus indirect) was dominated by indirect costs. Interestingly, indirect costs were not significantly higher in IBD patients than in a non-IBD control population; this might reflect the fact that the extensive (compared to non-Scandinavian countries) Danish welfare system is able to support IBD patients and absorb both income and health care expenses.~~

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A second Danish study by Vadstrup *et al.* (2020) was a national register-based study on incident CD and UC patients diagnosed between 2003 and 2015 that analysed the societal costs incurred within five years of a diagnosis, including the indirect costs of lost productivity.[27] In both CD and UC, the mean annual productivity losses per patient were highest in the first year after diagnosis and decreased in subsequent years (first year vs. fifth year: CD €3,990 vs. €3,155; UC €2,499 vs. €1,535). Productivity losses in the first year after diagnosis accounted for 31% and 37% of total costs in CD and UC, respectively and, together with hospital admissions, were the main cost drivers in the first year after diagnosis. In the subsequent four years, lost productivity (except for the second year in CD) exceeded all other costs and was the main cost driver among both UC and CD patients.

Two studies from the Netherlands have reported on indirect costs in IBD. The first study by van der Valk *et al.* (2014) was a multicentre study with voluntary patient participation.[28] The mean annual cost of lost productivity (including sick leave of patients and their caregivers) was €1,304 in patients with CD and €1,156 in those with UC; this represented 16% and 36% of total costs in CD and UC, respectively. The second study, by van Gennep *et al.* (2021), was cross-sectional and conducted in outpatient clinics at four hospitals in Amsterdam, again with voluntary patient participation, and it analysed the costs of overall work productivity losses (measured using the Work Productivity and Activity Impairment Questionnaire).[44] The mean annual cost per IBD patient for overall work productivity losses was €6,597, mostly attributable to presenteeism (€5,478), less so to absenteeism (€1,738). The highest overall costs for loss of work productivity were in patients using second or third classes of biological treatment (€8,756 and €19,468, respectively), while the lowest costs were in patients naïve to biologics and immunomodulators (€4,756). Significantly higher costs for overall losses of work productivity were found in patients with active disease, reduced health-related quality of life, severe fatigue, and active perianal disease (CD patients only).

In Spain, Aldeguer *et al.* (2016) published a retrospective, multicentre study using outpatient records from an administrative medical database of patients with UC diagnosed between 2002 and 2012.[29] The mean annual cost of lost productivity was €399, including €311 for sick leave and €88 for medical visits. Indirect costs represented 18.5% of the total costs. Factors impacting costs were age (negative effect), UC family history, diarrhoea, and psychological problems. The Swiss IBD Cohort Study (a national prospective cohort study recruiting patients from academic and non-academic centres across Switzerland), by Pillai *et al.* (2019), analysed the evolution of treatment and its related costs in the period 2006–2016.[30] The mean annual indirect cost per patient from lost productivity (absenteeism, as quantified using patient-reported data) was €1,339 in CD and €707 in UC. Indirect costs represented 12.3% of the total (direct plus indirect) mean annual cost per patient in CD, and 11.0% in UC. Annual indirect costs declined significantly by an average of 9% for CD and 28% for UC during the study period; however, this decrease was less marked after controlling for patient and disease characteristics, especially for CD.

In Italy, Benedini *et al.* (2012) conducted an observational, prospective, multicentre study of patients with CD between 2006 and 2010 and reported the annual cost of lost productivity to be €2,784, while for non-health care costs (transport, home assistance) it was €899.[31] These indirect costs accounted for 24% of the total costs. Rankala *et al.* (2021) investigated costs incurred through presenteeism and absenteeism in randomly selected patients with IBD living in the Turku University Hospital district, Finland.[45] The costs of absenteeism (€741) and presenteeism (€644) in IBD were found to be similar. The same was true for CD versus UC patients: absenteeism cost €724 in CD patients and €750 in UC patients, while presenteeism cost €763 in CD patients and €589 in UC patients.

In an Austrian study by Walter *et al.* (2020) of a very select patient population (members of the Austrian IBD Association), the mean annual indirect cost (absenteeism plus presenteeism) was determined to be €7,411.[46] Significantly higher costs were reported for patients with active disease (€12,377 vs. €6,040) and those being treated with biologics (€9,236 vs. €5,894).

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In a study from Poland, Malinowski *et al.* (2015) assessed the indirect costs in 2012 of absenteeism among patients with several autoimmune diseases, including UC.[47] Data on absenteeism (including sick leave, short-term disability, and long-term disability – whether temporary or permanent) were obtained from the Information System of the Social Insurance Institution (which does not cover all employed people). Three common macroeconomic indicators were used for making estimates: gross domestic product (GDP), gross value added (GVA), and gross income (GI). The mean annual costs of absenteeism per UC patient were €1,260, €3,034, and €928 according to GDP per capita, GVA per worker, and GI per worker, respectively. The majority of these costs were attributable to sick leave, at €787, €1,896, and €580, respectively.

Finally, Mandel *et al.* (2014) assessed the indirect cost of IBD due to disability/sick leave and presenteeism in Hungary.[48] Using the human capital approach, the cost of disability and sick leave was €1,450 and €430 per patient per year, respectively, with a total productivity loss of €1,880. The corresponding costs of presenteeism were €2,605 and €2,410 for CD and UC, respectively.

2.3.2 Asia

A single study from Japan by Yamabe *et al.* (2019) focused on the indirect costs of IBD.[49] This study was a retrospective, cross-sectional study that used pooled data of the annually fielded 2012–2014 Japan National Health and Wellness Survey. Respondents who self-reported IBD diagnoses were recruited via random sampling. Indirect costs were found to be 1·5-fold higher for patients with IBD than for controls (adjusted for baseline differences: 1,546,610 JPY vs. 1,067,331; $p<0·001$). Respondents with CD reported numerically higher absenteeism, presenteeism, overall work impairment, and activity impairment than respondents with UC. However, indirect costs were similar in CD and UC (1,645,068 JPY vs. 1,562,054, respectively; $p=0·766$).

2.3.3 North America

*United States*

There have been two reports using data from the Optum Health Care Solutions, Inc. employer claims database. These assessed indirect health care costs associated with UC in a privately insured, employed population in the US. A study by Cohen *et al.* (2015) for the years 2005 to 2013 evaluated the indirect use of resources, including lost productivity due to medically-related absenteeism and disability (both short- and long-term) during a one-year observation period.[40] The total adjusted indirect costs were, on average, twice as high for employees with UC than for non-UC controls (average annual cost: $4,125 vs. $1,961; $p<0·001$). Patients with moderate-to-severe UC had adjusted total indirect costs that were almost three times higher than those of controls ($5,666 vs. $1,960). A longer (1999 to 2017) follow-up study was published by Pilon *et al.* in 2020, with an observation period of around five years per patient. In this study, patients with UC incurred $2,142 more in total indirect costs per patient-year than non-IBD controls (UC, $5,307 vs. controls, $3,165); the respective cost difference for absenteeism was $1,002 (UC, $2,592 vs. controls, $1,590), and for disability it was $1,140 (UC, $2,714 vs. controls, $1,575). Over half of the costs of absenteeism ($558) were driven by outpatient visits alone (UC, $1,729 vs. controls, $1,140). In an analysis of indirect costs during the first 12 months after diagnosis, patients with UC incurred $2,214 more in indirect costs than non-IBD controls ($4,784 vs. $2,570), including $1,478 more incurred through absenteeism ($2,993 vs. $1,515) and $736 more because of disability ($1,791 vs. $1,055).

A study by Park *et al.* (2020), using data from the Optum Research Database from the years 2007 to 2016, estimated lost wages due to medically-related health care visits in patients with IBD.[39] The total mean annual estimated cost of lost wages in individuals with IBD was ~$3,000, and patients with IBD incurred approximately three-fold higher costs than their matched non-IBD controls (with an incremental indirect cost of ~$2,100). A novel study by Kahn *et al.* (2017) reported on productivity losses among 200 caregivers of paediatric CD patients using a large-scale, US employer-based health insurance database.[50] The annual productivity losses of caregivers of paediatric CD patients

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were 19·8% higher than those of controls (adjusted costs: $5,535 vs. $4,620). It was estimated that over the course of a CD patient's childhood (age 13·4 to 18 years) the cumulative productivity loss incurred by the patient's caregiver cost $24,118, versus $18,957 for control caregivers.

*Canada*

The 2018 Impact of IBD in Canada report provided the estimated indirect health-related cost of IBD in Canada for the year 2018 to be C$4,781 per IBD patient.[51] The authors arrived at this figure after extrapolating from data about sick days and disability from North American and European studies. This estimate comprises lost earnings related to sick days and disability, premature retirement and premature death, and out-of-pocket expenses. The average lifetime cost of wages lost to premature retirement among IBD patients in the workforce was calculated to be C$1,044,498 per CD patient and C$994,760 per UC patient. Elsewhere, data from Manitoba have demonstrated increased levels of presenteeism and the correlation between levels of disability and presenteeism and health care utilization.[52–55] Costs were not attached to these findings but, considering that levels of disability and some of these health care utilizations (like hospitalizations) are similar in Manitoba to other countries worldwide, costs could be assigned in a country-specific way.

2.3.4 South America

Two studies from Brazil focused on indirect costs in IBD. The first was a nationwide study by de S B Fróes *et al.* (2017) using the National Institute of Social Security (INSS) database, in which they calculated the costs of work disability.[56] Both temporary and permanent benefits were found to be higher in CD than in UC (temporary, $3,221 vs. $2,706; permanent, $5,698 vs. $5,077, respectively), but both showed a tendency to decrease between 2010 and 2014. The second study, by de S B Fróes *et al.* (2020), used the same INSS database to calculate the costs of work disability in patients with CD from a tertiary care centre in Rio de Janeiro between 2010 and 2018.[57] The average costs of temporary and permanent benefits were $3,340 and $6,638, respectively, which are comparable to those found in the earlier study.

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### 2.3.5 Summary

Indirect costs have been only incompletely researched. Further studies are needed that ~~address indirect~~address indirect costs other than lost work productivity, to more fully describe the substantial impact of IBD ~~has~~ on ~~sufferers~~patients. Nonetheless, the studies that are available suggest that indirect costs account for a substantial proportion of the total spent on patients with IBD, albeit with considerable variation between countries. Some of the differences between study results arise from diverse patient populations, distinct methodologies, and variations in the social support systems between countries. The most consistently identified drivers of indirect costs were active and more severe disease and comorbidities, including psychological disorders.

## 2.4. How Expensive Will IBD Be in the Future?

The cost of IBD in the future will be influenced by three main trends. First, the overall total costs will be affected by changes in the number of patients diagnosed with IBD. Second, mean and overall costs will be affected by changes in treatment patterns. Lastly, the price of the different interventions, and particularly the price of pharmaceuticals, will affect the overall costs.

### 2.4.1 Prevalence

Population-based epidemiological studies from North America and Europe have demonstrated the compounding prevalence of IBD over the past two decades.[2] Since 2000, prevalence increased by 3% and 4% per year in Canada and Scotland, respectively.[30,31] The prevalence of IBD was demonstrated to be ~0·5% of the general population in Canada, the US, and Scotland in 2010, is estimated to be ~0·75% in 2020, and is forecast to reach approximately 1% of the population by 2030.[32] Heterogeneity in the prevalence of IBD exists throughout the West; for example, the

prevalence in Portugal was only 0·1% in 2003, but has increased by ~5% per year, with the estimated prevalence having increased two-to-three-fold by 2019 and is forecast to be as high as 0·49% by 2030.[33] These data suggest the prevalence of IBD in the West could range between 0·5% and 1% over the next decade. Recent reviews of the literature also indicate that as the prevalence stabilizes in some countries, Asian countries that typically have had a lower prevalence are experiencing an upward trend. Altogether this points to a significant increase in the burden of IBD in the future. The increase in prevalence alone, if sustained at 3-4% a year, will lead to a doubling of health care costs between now and 2040.[34]

### 2.4.2 Trends in Treatments and Costs

In recent decades innovative new pharmaceuticals have led to changes in treatment for many patients with IBD. For instance, a study of patients with IBD based on individual-level patient data from the Medical Expenditure Panel Survey in the US concluded that the annual mean cost of treating an IBD patient nearly doubled between 1998 and 2015. Moreover, in the same period pharmaceutical expenses increased to become the largest cost driver, accounting for 44% of total expenditures.[35]

The cost of pharmaceuticals has increased the costs of treating patients, but could lower other costs. To the extent that new pharmaceuticals lead to improvements in the health-related quality of life for patients and delay the costs of disability, it will reduce the private and indirect public costs associated with IBD.

### 2.4.3 Trends in Prices of Treatments

The introduction of new pharmaceuticals will likely increase direct treatment costs initially, but as patents expire, the costs of pharmaceuticals will fall.[36] The introduction of new pharmaceuticals and biosimilars may also work to contain costs by increasing competition, but his effect seems to be stronger in Europe[37] than in the US.[38,39]~~The introduction of new pharmaceuticals will likely increase direct treatment costs, but as more competitors are introduced and biosimilars appear as patents expire, the costs of pharmaceuticals will fall.~~ In countries with a centralized system for buying and negotiating prices, this leads to large and immediate changes in costs. For instance, when the patent on adalimumab expired in Denmark in 2018, the authorities recommended the use of biosimilars. This resulted in a reported cost saving of 83%.[40]

Similar changes will occur in many countries in the future, but at the same time new, improved, and even more expensive treatments will also appear on the market. This will require the use of large-scale registries and improved, data-driven methods to quickly match patients with the best and most cost-effective pharmaceuticals.[41]

# 3. What Factors Drive Direct Costs in IBD Care?

## 3.1 Cost-Controlling Mechanisms

Besides the increasing cost of pharmaceuticals (both biologics and small molecule drugs), IBD costs are also driven by the quality, reliability, and equitability of IBD care. To ensure the delivery of high-value care, as well as economic sustainability, we need continuous evaluations of existing and new therapies, standardization of care practices, and greater efficiency.

~~As outlined in section 2, t~~The most ~~certain~~ obvious way to lower spending on IBD would be to reduce the burden of IBD. ~~In brief, if fewer people had IBD, and/or if people with IBD had less severe disease, spending on IBD would fall.~~ Reducing the incidence of IBD could partially be accomplished by environmental risk factor modification strategies at the population level. However, ~~In~~ in the absence of proven preventative strategies, the best way to reduce spending will most likely be to reduce the costs of treating IBD, such as by negotiating lower costs for medications.

Direct health care costs can be reduced either by lowering the price of a given health care service or by decreasing the rate at which that service is used (e.g., by restricting access to health care). These concepts are discussed below. Other ways of reducing costs include increasing non-physician IBD care (e.g., IBD nurse-led care or more extensive self-management plans) and eHealth, which reduces the cost per transaction. These are discussed in section 5.

While using price control regulations to lower the price of health care services may appeal to both providers and patients, there could be repercussions that lead to residual suffering on the part of patients. Lower prices for physician services may disincentivize providing care for IBD. In Ontario, Canada, the elimination of a premium paid to specialists for caring for IBD and other complex chronic diseases led to a drop in health care visits for those conditions.[42] This may have reduced costs without impairing quality of care if some visits were unnecessary. However, it might also have reduced access to specialists and negatively impacted quality of care. Similarly, lowering the price paid for drugs may discourage commercial innovators from investing in research and development; on the other hand, decreasing health care prices allows for health care to be delivered more equitably.

### 3.1.1 Controlling Costs by Lowering the Price per Transaction

Assuming a stable disease burden and steady demand for services, the cost of health care can be reduced either by imposing price controls or increasing competition among suppliers of those services. Price controls can be implemented by an external regulator, usually governmental, that imposes a maximum price for a drug or health care service, that is below the point where the price would be naturally set due to unencumbered market forces. The overarching purpose of a price control is to reduce costs for payers, allowing for the broader and more equitable distribution of the drug or health care service.

One of the major drivers of health care spending is the high price of innovator drugs. These prices are largely driven by the fact that most pharmaceutical innovators are granted a patent, during which time no competitors can sell an identical or similar drug. In order to improve access to innovative drugs, Canada, Australia, and most European countries have quasi-governmental boards that set a maximum price for a new drug. These boards set their prices by considering the needs of the population, as well as the prices of similar medications in that therapeutic space. Yet these panels must also take care not to set the price so low that companies are discouraged from continuing to invest in research and development. Additionally, many governments who are directly responsible for health care delivery will negotiate directly with pharmaceutical companies, demanding lower prices in exchange for access to a large pool of health care consumers.

Country-specific regulatory bodies generally impose limits on the duration of patents, after which time competitors can enter the marketplace. In Canada, the United States, the UK, and the EU, this period lasts for 20 years. The true period of market exclusivity is much shorter, as many years may pass between the time a drug is patented and when it receives regulatory approval. Once the patent expires, competitors are allowed to develop biosimilar or generic versions of the drug. In the last five years, patents have expired for infliximab and adalimumab in much of the developed world; as a result, there are currently four infliximab biosimilars and six adalimumab biosimilars approved for use. The regulatory requirements for approval of biosimilar medications are far less stringent than for bio-originator molecules, allowing these medications to rapidly enter the marketplace. This increased competition has led to substantial decreases in the list prices for biological medications. For example, adalimumab biosimilars were first approved for use in Europe in 2018, and in some European countries prices have since dropped by more than 50%.[43]

In contrast, the US does not have a board that sets a maximum drug price and, by law, prohibits government insurers (national Medicare and state Medicaid programs) from negotiating lower prices with pharmaceutical companies. Additionally, the US court system has been much more favorable to plaintiffs who have sought to maintain exclusivity and prevent entry of competitors into the marketplace; this has resulted in US consumers paying significantly higher prices than the rest of the developed world for IBD therapeutics.

Table 2~~3~~ lays out the great variation in costs of prescription drugs for IBD around the world. In individual countries there are differences in terms of the degree to which governments subsidize or provide financial coverage for medications. This high variability, especially for the costs of biologics in different places, underscores the potential lack of transparency in how pharmaceutical companies set their prices and, possibly, what other costs are added by governments or pharmacies.

**3.1.2 Lowering Costs by Reducing the Number of Health Care Transactions**

Health care providers can also throttle the ability of patients to access health care services in order to control costs. For people living with IBD, this can occur through several mechanisms such as ~~:~~

~~1.~~ ~~R~~requiring a patient or provider to demonstrate eligibility to access a drug or service, ~~.~~

~~2.~~ ~~D~~demanding patients provide payment of deductibles or co-pays, ~~.~~

~~3.~~ ~~C~~choosing not to provide or insure certain types of therapies or services, or ~~.~~

~~4.~~ ~~L~~limiting the availability of IBD care providers, facilities, or diagnostic testing, or cutting physician payments.

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In some countries, capitation leads to payments to IBD specialists being reduced. ~~Similarly, areas where governments have restricted the number of gastroenterologists can lead to longer wait times for people with IBD.~~ As a health care visit is frequently the trigger for requesting more expensive health care services (e.g., initiating biologics, ordering diagnostic testing), limiting access to specialists invariably leads to lower downstream costs, though likely at the expense of worse patient outcomes.

Eligibility criteria are commonly used by insurers and service providers to reduce access to IBD drugs, especially biologics and other advanced therapies. For example, many insurers will have tiered access to IBD therapeutics, only providing coverage for higher-tier medications to patients who did not respond to or were intolerant of more expensive options; this may include a requirement for patients to have used less expensive drugs such as azathioprine or methotrexate before a biologic will be prescribed. Several countries, such as the United Kingdom and Denmark, have regulatory bodies that provide guidance about the prioritization of medicines based on their efficacy and cost assessments. However, this approach still carries the risk of exacerbating the disease by mandating inferior treatments prior to initiating biologics. Similarly, providers may require the use of a biosimilar anti-TNF before coverage will be provided for an originator biologic, or mandate switches from originator drugs to biosimilars.

### 3.1.2 Identifying High-Need, High-Cost Patients with IBD

Another way that providers can lower health care costs is through interventions targeting high-need, high-cost (HNHC) patients. As with other chronic diseases, a small percentage of IBD patients account for a disproportionately large share of total health care costs.[44] Compared with other IBD patients, HNHC patients require far more care, particularly emergency department (ED) visits and hospitalizations.

A study from the US based on the 2013 Nationwide Readmission Database observed that a HNHC subset of IBD patients spent over 45 days in the hospital annually and accounted for 38% of total hospitalization costs (with median annual hospitalization costs ~$90,000 per patient) compared to a median of six days of hospitalization in the rest of the cohort.[45] Similarly, in the European Epi-IBD cohort, the 20% of patients with the highest costs during the first year after their diagnosis remained much more expensive throughout the five-year study than the remaining 80%.[11]

Patients at risk of progressing to HNHC remain difficult to identify with the models available.[46,47] Disease burden and drivers of health care usage are distinctly different in HNHC patients and are often amplified by behavioral health conditions and social risk factors, including psychiatric comorbidities, obesity, socioeconomic status and use of narcotics.[48] Some believe that the ~~drain~~ high expenditure on ~~on resources by~~ HNHC patients is preventable, or at least modifiable, through better disease control, coordination of care, preventative care and personalized interventions in the ambulatory care setting.[49–52] However, the majority of the data focus on readmissions following hospitalization or surgery and are based on electronic medical records and/or claims-based data that do not include the nonclinical risk factors necessary for building comprehensive risk management frameworks.

## 3.2 Appropriateness of Care and Improved Efficiency

As new options for treatment and prevention become available, it is important to demonstrate that any care being provided is appropriate, i.e., that its health benefits exceed its expected negative consequences. As resources are finite, health care providers generally seek to deliver services that provide the greatest reduction in disease burden at the lowest possible cost, a concept known as 'cost efficiency.'

### 3.2.1 Variability in Care and Standardizing Care to Facilitate Appropriate Health Care Delivery

Variability in care is a key barrier to achieving appropriate care in IBD.[53] Quality indicators can be used to objectively measure quality of care in chronic diseases and provide measurable standards for clinicians.[54,55] They are essential in identifying the magnitude of variability in care and monitoring improvement and, thus, for closing the gap between ideal and actual clinical performance.[56]

Often, clinicians may not realize that they are over-investigating patients, providing superfluous or harmful treatments, or applying high-cost treatments in an outdated or misinformed way. For example, the continued use of mesalazine in patients starting either immunomodulators or biologics is common but appears to be of little clinical benefit.[57,58] Additionally, the methods and frequency for monitoring IBD patients using blood and stool samples are not always evidence-based and sometimes unnecessary[59]. While there are limited data available to prove the economic consequences of inappropriate care in IBD, it is widely recognized that variability in care is a significant problem that raises direct and indirect costs.[60,61] Yet, very few electronic medical record systems document care in a way that gives clinicians, patients and/or providers the ability to monitor care quality in a way that provide mechanisms to enable visibility of unwarranted variation.[62]

Evidence-based clinical pathways are one strategy for standardizing care, improving appropriateness, and reducing variability in care, and thereby improve outcomes and reduce costs; but they are often complex, out of date, lack credibility, or poorly implemented.[63,64] Suboptimal adherence to international, evidence-based guidelines is an ongoing problem across various aspects of IBD care.[65–67] Clinician engagement, staying up-to-date with the research, and strategies to improve uptake are imperative if clinical pathways and guidelines are to improve the appropriateness of IBD care delivery. The best way of implementing international guidelines in clinical practice has yet to be proven but minimizing variability by regularly updating clinical algorithms could represent one way to help standardize care.

**3.2.2 Delivering Efficient Care**

Efficiency is the allocation of available resources in a way that provides the best outcomes for the community. Inefficient care drives up costs. Vast sums are spent on health interventions that are irrelevant, redundant, or excessive; that provide few or no benefits; or that in some cases cause harm. In IBD, reactive, crisis-driven care has been correlated with higher costs than proactive (pre-emptive) care.[68] Patients in remission have the lowest costs of care and highest quality of life; patients responding to treatment have lower costs of care than patients with high disease activity who are not responding to treatment. Recent data suggest that the consequences of inefficient or low-value care are reflected in the indirect costs of lost productivity.[24,69,70] Thus, the total costs of care are more likely to be reduced by treatment that is effective and care that is efficient.[71,72]

**3.2.3 Integrated Health Care Models**

According to the WHO, integrated care models, encompassing a biopsychosocial approach to care, are the optimal way to standardize the management of chronic diseases such as IBD.[73] A multidisciplinary team approach to managing IBD is a central component of IBD care owing to the complexity of the disease, which is associated with extra-intestinal manifestations and complications needing specialist care.[74] While the members of the multidisciplinary team vary, accordingly to the complexity of care being delivered and the individual patient's needs, for the sake of efficiency it should include at least an IBD specialist-gastroenterologist, a surgeon, a radiologist, a pathologist, an IBD specialist nurse, a dietitian, and a pharmacist, with the option of specialists in psychology, dermatology, rheumatology, and ophthalmology.[75–77] A dedicated, multidisciplinary IBD service has been found to improve patients' psychosocial functioning and reduce hospitalizations and inpatient care, thereby increasing efficiency, even after accounting for the additional costs of the psychologist, social worker or dietitian etc. needed on the team.[78,79,80]

**3.2.4 Participatory Care Models**

Participatory health care models involve a collaboration between patient and physician and refer to a shift in which patients move from being merely passengers to co-pilots of their own health care. Participatory medicine promotes shared decision-making and facilitates patients' self-management of their disease. Digital health or eHealth tools incorporate a component of patient self-management whereby patients share information about their IBD with a program or health care team, from which patients can adjust their therapy based on algorithms.[81] This approach uses virtual clinics and has been found to reduce outpatient visits by up to 20%.[82] eHealth platforms, which facilitate participatory care models and support remote patient monitoring, have demonstrated improvements in disease activity, quality of life, quality of care delivery, and reductions in health care expenditure via reductions in outpatient visits, ED visits, and hospitalizations.[83] Constant Care in Denmark, and MyIBDCoach in the Netherlands, are web-based tools developed for remote IBD monitoring that have taken a participatory approach to integrated IBD care, focusing on disease activity, psychological wellbeing, preventative care, and the quality of care indicators. Compared to standard care, remote monitoring resulted in a significant decrease in outpatient visits and hospital admissions, improved quality of care, and significantly reduced the costs of care.[84–87] These early data suggest that participatory health care models have the potential to improve the appropriateness and efficiency of IBD care.

### 3.2.5 Population Health Management

Population health management (PHM) is an emerging concept within the field of IBD that can be defined as the coordination of care at a macroscopic level to improve outcomes and effectively manage both clinical and financial risk for patients.[88] PHM aims to improve quality of care, improve population health outcomes, and reduce health care costs by incorporating chronic care models, data sharing, shared decision-making, and risk profiling into population management goals.[44,88] However, the extent to which PHM models can improve the appropriateness and efficiency of IBD care remains to be seen.

## 3.3 Inequality in Access to Care

Ethnicity and socioeconomic status (SES) are major contributors to health disparities, and unfavourable SES has been associated with poorer health outcomes and shorter life expectancy. It is therefore essential to account for these specific determinants when analysing a population's access to, and use of, health care resources. Access to care among socioeconomic minorities ~~suffering~~ living with ~~from~~ chronic diseases such as diabetes or rheumatoid arthritis has been studied for several decades and the disparity in access to care is a major reason for poorer health in those populations. In particular, a lack of long-term follow-up and higher rates of ED visits have been highlighted in disadvantaged social groups.[89]

In IBD, inequalities in access to care have been identified, as well. For example, diagnostic delay, defined as the time from first symptoms to diagnosis, may have an important impact on clinical management and prognosis. Median diagnostic delay varies between countries but is generally longer for Crohn's disease (median range: 4 to 9·5 months) than for ulcerative colitis (median range: 1 to 4 months).[90–93] Lower levels of education have also been associated with a longer diagnostic delay[93]. Once a diagnosis is established, patients may face additional delays in the management of their disease. A Canadian study demonstrated that lower-SES patients had a higher risk of delayed IBD-specific therapy after their diagnosis, as well as a higher risk of long-term non-use of an IBD-specific drug.[94] A subsequent study from Manitoba, Canada showed that people of lower SES had higher rates of hospitalization, longer hospital stays, and higher mortality, even though there was no apparent difference in their ability to access IBD-specific medications.[95] Variability was found in the use of steroids and immunomodulators, with fewer given to those of a non-white ethnicity or lower income.[96,97] Greater use of biologics was associated with higher SES, and access to biological treatments has been found to vary according to ethnicity. Two studies conducted in the US showed that African American patients were less likely to be prescribed infliximab.[98,99] Similar observations were found in Leicester, UK with a lower use of biological therapies among Asian patients than non-Asian, primarily Caucasian, patients.[100] However, access to drug treatments among ethnic minorities remains difficult to study, largely due to a lack of data, which usually relies on patient self-reporting rather than prescription databases. Self-reporting may confound any results due to non-adherence to therapy or providers' cost-reducing strategies for prescriptions.

No significant differences have been reported in accessing surgical interventions based on SES or ethnicity. However, a single study has found that a laparoscopic approach to colectomy was more often used in patients with private insurance than those with government-subsidized Medicaid insurance coverage (43% vs. 23%), suggesting that private insurance may increase access to less invasive surgical techniques, as well as specialized surgical consultations.[101] There could also be systemic cognitive bias driving surgical decision-making in certain clinical scenarios for IBD patients.

Rates of hospital admissions and ED visits have also varied according to insurance status. In the US, ED visits have been found to be 6.6 times more frequent in patients covered by Medicaid;[102] rates of ED visits were also higher for patients without health insurance.[103] These data suggest that low-income status is associated with an increased risk of not being able to access timely and

effective care, which may impact long-term health, disease prognosis and, ultimately, costs. These findings are supported by a recent study demonstrating that IBD patients have more IBD medication prescriptions and fewer ED visits when followed at a US tertiary referral centre than at community hospitals, indicating possible differences between secondary health care systems and tertiary-oriented IBD subspecialty practices.[104] Higher rates of hospitalization have been found in African American IBD patients, with almost a threefold increase in patients covered by Medicaid, as compared to other types of insurance.[102] In a study from Manitoba, Canada people with IBD who attended the ED and were not seen by a gastroenterologist were less likely to be seen by one during follow-up.[105] These ED visits incurred an extra cost of $1 million per year for a system that provides ED services for approximately 800,000 people.[106] This money could be allocated to a better care model, as outlined above. Finally, a Danish study identified greater difficulty for IBD patients to obtain life insurance compared to the general population, with the most common issue being a marked increase in premium weighting.[107]

These observations all point to a greater financial burden for lower-SES groups, and many questions about the influence of health insurance systems. We need a deeper, real-world understanding of how patients' lives, and the resources they access, may be shaped by gender, ethnicity, and SES, and how these drivers affect health outcomes (Figure 3). The study of other factors determining patients' access to care, such as travel distance to health services and out-of-pocket expenses, would also provide additional insight into the obstacles that patients face.

### 3.4 ADHERENCE

Patient adherence to treatment programs remains a critical element of successful disease management. The rate of non-adherence to medical treatment in IBD is around 50%, resulting in negative impacts on clinical outcome, morbidity and cost.[108] Adherence is important for prescribed treatments but also for disease monitoring. While it is recognised that chronic diseases are associated with suboptimal adherence, especially if the disease is in remission, a direct evaluation of outcomes has been more difficult to make. Not all physicians consider the relevance of adherence in their practice and even fewer use objective measures to quantify it, despite the widespread acknowledgment of its importance.[109]

Assessing adherence to oral medications with objective instruments is not easy and medication collection rates and self-reported questionnaires are the most frequently used methods. However, adherence to infusion-based biological therapies has been reported. In a retrospective study of 193 IBD patients, remission as measured by faecal calprotectin <100 ug/ml and CRP <5 mg/ml was strongly associated with adherence. Predictors of non-adherence were being male, shorter IBD duration and clinic non-attendance.[110] In a recent multicentre, cross-sectional study, subcutaneous administration was significantly associated with inadequate adherence to biologics (OR 4·8, 95%CI 1·57-14·66).[111] Elsewhere, in a claims database study of patients with IBD or rheumatoid arthritis, adherence was better for infusion-based biologics than for oral agents.[112]

A systematic review of risk factors for non-adherence to anti-TNF therapy identified being female, smoking, anxiety, and "moodiness."[113] In one tertiary centre study, a Crohn's ~~CD diagnosis~~disease diagnosis, insurance type, psychiatric history, smoking, prior use of biologics, and current use of narcotics were significantly associated with an increased risk of non-adherence;[114] adherence dropped to 42% when four of these risk factors were present. Adherence was significantly greater for more advanced therapies, with non-adherence occurring in 35·1% of 5-aminosalicylate users, 18·3% of thiopurine users and 7·4% of biological users. Patient beliefs about medication necessity and concerns about medication toxicity were the most important predictors of adherence.[115] A study from Spain of 234 patients treated with biologics found that 10% of them postponed hospital infusions and 5% delayed collection of subcutaneous vials at the hospital pharmacy.[116]

Interestingly, medication adherence in pregnancy differs among drug classes. In a Canadian study using administrative data, almost one-quarter of women with IBD who were previously adherent to medical therapy were not adherent during pregnancy. Women were more likely to be adherent to biologics than thiopurines and 5-aminosalicylates within their first trimester.[117] The perception that IBD medications may adversely affect child development during pregnancy is quite common and up to 22% of females believed that the risk of adverse events was greater than the risk of disease relapse. There is an urgent need for pre-conception counselling to ensure women with IBD receive proper treatment during pregnancy.

High levels of patient activation – defined as having the knowledge, skills, and confidence to effectively manage one's own care – have been associated with improved outcomes in many chronic illnesses. Anxiety and depression have been implicated in decreased patient activation, while those with high activation were more likely to be in clinical remission at follow-up.[118] Structured interventions are vital, especially in high-risk patients. Preventative measures through telephone nurse counselling and the use of reminder systems, as well as the identification of patients at risk, could help to improve adherence to treatment.

The chronic and progressive course of IBD creates psychosocial discomfort for patients, so interventions are necessary at each step of treatment, beginning with their diagnosis and throughout long-term follow-up. For example, in Italy an agreement was reached in 2020 by a patients' association, the Catholic University, and the Istituto Superiore di Sanità to identify effective interventions for ensuring the highest degree of psychosocial assistance.[119] They determined that a multidisciplinary and coordinated team with integrated home-based assistance was the key to achieving the best quality of life. Patient engagement is essential in this process for ensuring adherence.

# 4: COST-EFFECTIVENESS IN INFLAMMATORY BOWEL DISEASES

## 4.1 LIMITATIONS OF RANDOMIZED CONTROLLED TRIALS

The randomized controlled trial (RCT) is considered to be the gold standard of biomedical research and there has been an exponential rise in published RCTs, and systematic reviews and meta analyses of RCTs, over the years.[120] RCTs are highly suited to comparing two or more similar treatments in a double-blinded setting, e.g., two different drugs or a placebo and a drug. At the same time, the past two decades have seen a shift in RCT endpoints used when studying IBD. This shift has been made possible thanks to the introduction of biological agents targeting specific cell types or cytokines. Approval of the first two anti-TNF agents, infliximab and adalimumab, relied on clinical response and clinical remission (based on the Crohn's Disease Activity Index (CDAI)), as clinical endpoints. Regulators have become more stringent in recent years, requiring endpoints that now include steroid-free remission and endoscopic improvement; but drug approval still largely depends on pure efficacy endpoints. Currently, regulators ask for co-primary endpoints including clinical remission and endoscopic response. Histological improvement in ~~UC~~ulcerative colitis, and transmural healing for Crohn's disease~~CD~~, are now secondary endpoints and pave the way for new concepts of histo-endoscopic healing, mucosal healing, and disease clearance that combine clinical, endoscopic, and histological endpoints.

Although valid for drug development, there are a number of drawbacks to RCTs. First, they demand strict inclusion criteria, creating homogeneous groups to ensure high internal validity (the extent to which the observed results represent the truth in the population studied). However, the strictness of these criteria means the results cannot always be extrapolated to the general population (i.e., achieve external validity).[121] The general population can include paediatric, elderly, or pregnant patients, and those with or at increased risk of comorbidities such as infection, cancer, or cardiovascular disease, and certain ethnic groups.[122] Furthermore, there is variability in the background risk of infection worldwide, meaning that decisions around the cost-benefit of immunosuppression, in particular, will differ. In a cross-sectional study within the IBD Partners cohort reported by Johnson et al. (2020), only 7·6% of patients from a total of 14,747 patients with IBD reported RCT participation at any time.[123] The factors which were predictive of participation in a RCT were having Crohn's disease ~~CD~~ (more so than having ~~UC~~ulcerative colitis), having more severe disease (including previous surgery, treatment with biologics), and being followed at an academic institution. In the case of IBD, RCTs will typically exclude specific subpopulations, such as isolated proctitis, patients failing several lines of biological therapies (who are considered to be too refractory), patients older than 75, those planning pregnancy, and patients with previous cancers and/or concomitant disorders. In a retrospective cohort study of adult IBD patients seen at a tertiary referral centre, only 31% of patients would have been eligible to participate in a RCT. The most frequent reasons for not being eligible were stricturing or penetrating Crohn's disease~~CD~~, high doses of steroids, and comorbidities or prior exposure to biologics.

The fact that many patients with moderate-to-severe IBD do not qualify for enrolment in RCTs raises questions about their external validity beyond the clinical trial populations.[121] At the same time, these challenges offer an opportunity, once a drug has been approved, for real-world studies in less restricted patient populations. Despite a sharp increase in the number of active RCTs, recruitment rates have decreased in recent years. These recruitment challenges prolong the drug approval process and put investigators at risk of so-called 'trial-fatigue.' The fall in recruitment rates could be linked to the greater administrative burden associated with RCTs, and/or a greater burden on patients (in the case of IBD, the mandatory ileo-colonoscopy at baseline and at the primary endpoint, as well as other examinations such as cardiac exams, ophthalmology and neurological work-ups, MRI, etc.) and stringent inclusion criteria. To improve recruitment rates, pharmaceutical companies are therefore expanding activities to new countries and continents such as Eastern Europe, South America, Russia, Asia, and India. Large community hospitals with the required staffing and setup for clinical trials are also a means for increasing recruitment rates.

Generally, most RCTs in IBD do not consider economic endpoints, although these would provide a useful additional dimension. The follow-up period in most RCTs is only long enough to measure the added cost of therapy in the short term but may not capture the full benefits of a new therapy over time. When including cost-effectiveness models in the design of a RCT, assumptions about the long-term efficacy and safety of a drug are needed, yet are often difficult to make. However, with more drugs being approved for IBD, incorporating cost-effectiveness analyses during RCTs may provide meaningful improvements in outcomes.

## 4.2 What Do We Know about the Cost-effectiveness of Treatments in Inflammatory Bowel Diseases?

Chronic diseases are the leading causes of illness, disability, death, and of growing health care spending in high-income countries. As a consequence, policy makers and health care professionals are becoming increasingly concerned about containing health care costs while improving the quality of patient care. Most of the available data focus on assessing cost-effectiveness, i.e., the extent to which the inputs used to produce a given output are minimized (productive efficiency). However, this does not indicate whether the right mix of health service outputs is being produced (allocative efficiency), or whether the right decisions are being made about how to use resources to maximize health and wellbeing over time (dynamic efficiency).[124] Several interrelated challenges must be overcome to build and analyse cost-effectiveness models of chronic diseases.[125] First, chronic diseases are much more prolonged than acute conditions and interventions to slow their progression may reduce complications years, or even decades, after the interventions (and their costs) occur.

Second, the duration of chronic diseases means that it can be costly and impractical to conduct clinical trials that directly test whether an intervention improves outcomes. When clinical trials are not feasible, simulation models are an attractive alternative for making predictions about likely cost-effectiveness. The need to develop simulation models leads to another major challenge: chronic diseases are usually complex, with progression depending on multiple risk factors that can produce widely varying complications. As a result, developing a cost-effectiveness model often focuses on disease progression. Clinical trials may provide evidence of an intervention's effects on intermediate outcomes, but it is then up to the disease progression model to simulate long-term outcomes.

Third, identifying the costs of complications in chronic disease modelling often receives inadequate attention compared to the time and effort devoted to modelling disease progression. Costs of averted complications cannot typically be estimated during a trial because these complications mostly begin to manifest years after the intervention.

Much uncertainty surrounds the relative cost-effectiveness of treatment options for IBD. Trials of the sufficient size and duration needed to answer the question of long-term cost-effectiveness have not been carried out and might never be. In addition, cost-effectiveness studies that do exist may not necessarily be transferable to other health care settings. The few studies we do have rely mostly on observational data of cost profiles before and after a specific intervention What follows is a summary of the available literature. A bibliographical search was performed in PubMed from inception up to February 2021 using the terms 'inflammatory bowel disease' or 'Crohn's disease' or 'ulcerative colitis' combined with 'cost-effectiveness' or 'cost-effective' and 'review' or 'meta-analysis.'

### 4.2.1 Immunosuppressive Treatment

*Methotrexate*

Mlcoch *et al.* evaluated the cost-effectiveness of parenteral methotrexate compared to standard care (i.e., high doses of oral corticosteroids followed by gradual tapering) for the treatment of mild-to-moderate Crohn's ~~CD in~~disease in the Czech Republic.[126] The authors developed a three-year

Markov model and over a three-year time-horizon methotrexate yielded an additional 0·111 quality-adjusted life-years (QALYs) at an additional cost of €513, with an incremental deterministic (probabilistic) cost-effectiveness ratio of €4,627 (€4,742)/QALY, far below the willingness-to-pay (WTP) threshold (≈ €47,000/QALY). The authors concluded that parenteral methotrexate proved to be cost-effective in patients with mild-to-moderate Crohn's disease~~CD~~.

*Thiopurines*
Vasudevan *et al*. assessed the cost-effectiveness of initial immunomodulators and anti-TNF agents for the treatment of Crohn's ~~CD from~~disease from a US third-party perspective, incorporating current treatment algorithms, optimization strategies, and the lower costs of biosimilars.[127] A one-year Markov model was developed to simulate the cost and QALYs of initial azathioprine, infliximab, and combination therapy for moderate-to-severe Crohn's disease~~CD~~. Initial azathioprine had the lowest cost and utility ($35,337 and 0·63 QALYs), while combination therapy was the costliest yet conferred the greatest health benefits ($57,638 and 0·67 QALYs). The authors concluded that in the era of biosimilars, initial azathioprine with escalation to infliximab appeared more cost-effective in the short term compared with infliximab or combination therapy, although initial combination therapy yields acceptable incremental cost-effectiveness ratios (ICERs) in the long term, with ongoing reductions in anti-TNF therapy costs, and will likely be the preferred treatment strategy in the future.

Vasudevan *et al*. performed a systematic review of economic analyses of strategies to optimise immunosuppressive therapy for IBD.[128] They then produced a qualitative synthesis of the studies identified, finding that both thiopurine methyltransferase (TPMT) testing before commencing thiopurines, and thiopurine metabolite testing for dose optimization, were cost-effective.

### 4.2.2 Treatment with Biologics
*Anti-TNF treatment*
In 2009, Bodger *et al*. assessed the cost-effectiveness of infliximab and adalimumab for Crohn's ~~CD within~~disease within the UK's NHS.[129] The model suggested acceptable ICERs for biological agents when considering a lifetime horizon with periods of up to four years of continuous therapy. In 2011, Bodger *et al*. reviewed the cost-effectiveness of treatments for IBD and showed that for Crohn's ~~CD cost~~disease cost-utility models for anti-TNF drugs versus standard care consistently demonstrate incremental benefits, albeit it with an increased cost overall.[130] Pillai *et al*. performed a systematic review to assess the cost-effectiveness of treatment strategies for IBD.[131] They found that while biological agents helped to improve outcomes, they had high costs and were therefore not cost-effective, particularly when used as maintenance therapy. The authors noted that the cost-effectiveness of biological agents might improve as market prices fall with the introduction of biosimilars (their review was published in 2017).

Whether early biological therapy is more cost-effective than conventional therapy for Crohn's ~~CD in~~disease in adults is unclear due to a limited number of studies, insufficient data on endoscopic remission, and the heterogeneity of existing studies. Thomson *et al*. reviewed this topic and found that top-down therapy improved quality-adjusted life expectancy and reduced costs when compared to step-up therapy.[5,132] After one year the incremental cost-utility ratio was €92,440/QALY, while after four years it was €1,462/QALY. The authors conclude that early treatment with biologics does not have an obvious clinical benefit over conventional (step-up) therapy, despite some studies suggesting otherwise.

Vasudevan *et al*. performed a systematic review of economic analyses of strategies to optimise anti-TNFs for the treatment of IBD.[128] They then produced a qualitative synthesis of the studies identified, finding that multiple tailored approaches to treatment based on objective markers of disease activity or efficacy have been shown to be cost-effective in Crohn's disease~~CD~~, including following secondary loss of response to anti-TNF therapy for postoperative recurrence and in escalating treatment.

*Vedolizumab*
The current literature suggests that from a cost-effectiveness perspective vedolizumab might be a reasonable option for first- and second-line therapy for moderate-to-severe ulcerative colitis~~UC~~.[133] To date, there are no studies to suggest that vedolizumab would be the most cost-effective option for first-line therapy for moderate-to-severe Crohn's disease~~CD~~. However, studies suggest that vedolizumab could play a role later on in an individual's treatment course.[133] More studies are warranted to evaluate the comparative effectiveness of other biologics, as well as more recent advanced, targeted immunological therapies.

#### 4.2.3 ~~Future Research Agenda~~Summary

~~Many~~ Several cost-effectiveness analyses, summarized in several systematic reviews and meta-analyses, have been performed for IBD (Table ~~4~~3), most of which focus on anti-TNF treatments. Studies of varying design have produced a wide range of incremental cost-effectiveness estimates, which highlights the challenges and limitations of existing modelling techniques. Prices of originator drugs as well as the need for long-term treatment to maintain remission have led to most studies concluding that biologics are currently not cost-effective despite their proven efficacy. The cost-effectiveness of biological agents may improve as market prices fall and with the ongoing introduction of biosimilars. Our literature search also demonstrates that cost-effectiveness studies remain an area with room for improvement as ~~-~~studies evaluating the cost-effectiveness of drugs other than anti-TNFs (such as vedolizumab, ustekinumab, or tofacitinib), especially comparative studies with other drugs, are lacking despite some of them having been on the marked for several years.

Future research should identify optimal treatment strategies that reflect routine clinical practice and that incorporate indirect costs, new endpoints (such as endoscopic healing), and lifetime costs and benefits, all while taking into account the reduced cost of biosimilars. Additionally, ~~A~~as cost-effectiveness estimates may change in both directions with fluctuations in prices, cost-effectiveness studies are at risk of becoming outdated if not regularly maintained. ~~Finally, more studies evaluating the cost-effectiveness of drugs other than anti-TNFs (such as vedolizumab, ustekinumab, or tofacitinib), especially comparative studies with other drugs, are needed.~~

### 4.3 Are the Data Sources Available Adequate to Assess Cost-effectiveness?

Cost-effectiveness analyses are available on all advanced therapies; in some countries these studies are mandatory and also serve as the basis of reimbursement approval, while other countries have no such requirements. One of the most pressing limitations of these cost-utility analyses is that the drug and service costs are representative for the given country/region, but the outcomes and disease state transition probabilities used in Markov models are calculated from the landmark clinical trials. However, disease characteristics in real-world cohorts can significantly differ from that of RCTs, especially in Crohn's disease~~CD~~.[121] In some countries, prices for drugs and services can vary widely depending on patients' insurance plans (e.g., in the US). Thus, the local reimbursement environment is a significant confounder, and results from these studies cannot be directly extrapolated to different countries. Another limitation is that pharmacoeconomic analyses have validity only in the short term, since conclusions may change significantly with movements in drug/service reimbursement prices. Furthermore, the results are dependent on how the model is built (e.g., were indirect costs included and, if so, how detailed were the calculations?). For example, a very recent cost-effectiveness analysis from the UK concluded that although ferric carboxymaltose was the most effective iron supplementation therapy, its use was associated with a direct cost increase of 2,045 GBP per additional responder; however, indirect costs such as productivity losses were not calculated.[134] Similarly, a Swiss group[131] concluded in a systematic review based on 24 Crohn's ~~CD and~~disease and 25 ulcerative colitis~~UC~~ studies that maintenance biological therapies were not necessarily cost-

effective, yet were associated with improved outcomes. In the future, cost-effectiveness studies need to be based on high-quality, real-world IBD cohorts to more accurately estimate disease outcomes[135]; ideally, better estimates of indirect costs would also be used.

Despite the abundance of cost-effectiveness reports based on extrapolations from landmark clinical trials, most clinical trials allow only a few patients representative of real-world patient populations to be included[121] and measure failure endpoints that do not resemble the real world. Furthermore, there is a significant imbalance in the geographical diversity of these data. Unsurprisingly, most data originate from North America and Western Europe, while far fewer data are available from other parts of the world (Table 34). Some data are available from Eastern Europe and Saudi Arabia, but largely missing from Asia, South America, Africa, or have been presented in abstract form only. Similarly, significant inequities in access to health care and biologics have been reported worldwide that have not been explained by epidemiological factors, drug prices or health care expenditures (e.g., in Eastern European countries). Cost-effectiveness, cost-utility and studies investigating access to advanced therapies could help alert decision-makers and result in more equitable reimbursement policies that ultimately lead to better access to biological therapies.

Another confounder in cost-effectiveness reports is cohort type. Patient cohorts from RCTs and referral IBD centres overestimate the probability of severe disease phenotypes and may report higher probabilities of outcomes (e.g., the need for advanced therapies, hospitalizations, surgeries, etc.). A more balanced analysis may be to base the models on RCT/referral centres and then re-run the analysis on high-quality, population-based inception cohort datasets. The two models are not mutually exclusive, but rather complementary. While the first represents the reality of referral centres, the second scenario is more appropriate for estimating the situation at a regional level. One example of such a study is the recent cost-effectiveness analysis of a European population-based inception cohort.[11]

The third input for cost-utility analyses, after costs and transition probabilities, is that of utilities. These measures of patients' perception of overall health status and preferences were traditionally derived from time-intensive processes (the standard gamble or the time trade-off), but in recent years have been derived from the EuroQol five-dimension questionnaire (EQ-5D) or the Short Form 6D (SF-6D).[136–138] Utilities are often derived prospectively in RCTs and are therefore subject to the same biases that have been pointed out with costs and transition probabilities — can these measures from highly selective patient populations be extrapolated to the real world?

Another potentially fruitful topic is the assessment of therapeutic sequencing, instead of assessing different therapies alone. Very few studies are available that report the comparative cost-effectiveness of early versus later therapies or sequencing of biological therapies.[139] For example, in 2017 a group led by Hungary evaluated the best sequence of biological therapies after the entry of biosimilars onto the market in nine different Western and Eastern European countries in luminal and fistulizing Crohn's ~~CD based~~disease based on economic considerations.[11] The conclusion was that biosimilars appeared to be the most cost-effective treatment, followed by using adalimumab and vedolizumab therapies, but there was a wide variation between the costs across the countries.

Most studies have concluded that biologics, despite their high costs, are cost-effective for the treatment of moderate-to-severe IBD. However, further research is needed from underrepresented regions. Furthermore, data based on outcomes from high-quality, real-world cohorts would likely better represent any cost-effectiveness that does exist. We need more research on estimating indirect costs, ideally based on real-world cohort studies (i.e., that include disability, absenteeism, presentism, etc). Future cost-effectiveness studies should look beyond simply assessing medical therapies and could investigate different treatment algorithms (e.g., early vs. late medication, medication sequencing, medical vs. surgical approaches for a specific scenario). In addition, a new

wave of studies is approaching that will place greater emphasis on value-based care delivery instead of the more traditional cost analyses.[140]

## 4.4 Is Monitoring Disease Activity and Drug Concentrations Cost-effective in IBD?

### 4.4.1 Monitoring Strategies

Recently, the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE-II) initiative of the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) identified short, medium- and long-term targets for treatment based on a systematic review and expert consensus.[141] This work provides not only a framework for selecting targets, but also monitoring whether or not the targets are being met. Indeed, monitoring targets and responding appropriately are a vital part of the treat-to-target paradigm. STRIDE-II provides a framework for determining cost-effectiveness based on specific treatment targets and should be considered in future cost-effectiveness studies.

At present, endoscopic healing (and more recently histological healing for ulcerative colitis~~UC~~) is seen as the best treatment target for IBD patients, albeit with a degree of uncertainty around the definition of 'optimal' or 'deep' healing and a lack of data suggesting that changing therapy in patients with a partial response leads to improved outcomes. Repeated endoscopic monitoring is invasive, expensive and not without risk.[142] Therefore, non-invasive biomarkers that reflect endoscopic inflammation are attractive if they reliably reflect mucosal inflammation, are rapidly available to aid in decision-making, are cost-effective and reproducible.[143]

### 4.4.2 Short-term Target Monitoring

Although patients will appreciate the long-term benefits of mucosal healing such as fewer hospitalizations and surgeries and less disability, symptom relief is usually front of mind. This can be readily monitored using a range of patient-reported outcome measures (PROMs) such as the HBI, PRO-2, or CD-PRO for Crohn's ~~CD and~~disease and the SCCAI, PRO-2, or UC-PRO for ulcerative colitis.[144–148] Composite scores such as the CDAI and Truelove and Witts Severity Index combine clinical and laboratory data, while the Mayo score and others combine clinical and endoscopic data.[149–151] The benefits of symptom monitoring are the speed, low cost and alignment with patient priorities when they are experiencing active disease. However, there are significant limitations to solely monitoring and palliating symptoms for IBD patients. There is a poor correlation between symptoms and endoscopic inflammation, particularly in patients with small intestinal inflammation.[152] Even in the absence of symptoms, mucosal inflammation is associated with long-term complications, hospitalizations and surgeries.[153]

C-reactive protein (CRP), a serum marker that is cheap and readily available, has been shown to have a modest association with endoscopic inflammation, albeit more so in Crohn's ~~CD than~~disease than ~~UC~~ulcerative colitis.[154] CRP has a higher specificity but lower sensitivity than faecal calprotectin (FC), suggesting that monitoring CRP early after treatment escalation gives a useful, if blunt, assessment of endoscopic inflammation.[155] Yet despite widespread clinical use, there are no cost-effectiveness studies to support the use of CRP for IBD monitoring.

### 4.4.3 Medium-term Target Monitoring

That FC is a more sensitive measure than CRP means that after a change in treatment FC will more accurately reflect mucosal healing. In the CALM study, symptom and biomarker (CRP and FC)-driven treatment escalation led to higher rates of endoscopic healing than symptom-driven escalation alone.[156] Post hoc analysis demonstrated that most of the treatment escalation in the biomarker symptom group was driven by high FC rather than CRP, suggesting that FC is a useful target and indicative of endoscopic inflammation.[141] Its cost-effectiveness was demonstrated in a UK analysis of the tight control arm using adalimumab escalation.[157] For children, resumption of normal growth is a key target and easily monitored biomarker of health.

#### 4.4.4 Long-term Target Monitoring

Endoscopic healing, evaluated by ileocolonoscopy, is an important target in clinical trials, yet its role in a real-life setting among patients with a partial response remains uncertain. Ileocolonoscopy cannot be carried out repeatedly due to patient resistance and its high cost. Therefore, its judicious use in combination with PROMs and biomarkers is best, especially when important treatment decisions need to be made. Deep remission, comprising endoscopic and clinical remission, has also been shown to impede Crohn's disease~~CD~~ progression.[153] Monitoring quality of life and disability are also essential in the long-term. However, patient variables (e.g., mental health, comorbidities) and disease variables (e.g., fibrotic strictures, bile acid malabsorption) other than inflammation can affect both constructs and need to be investigated.

In addition to the targets endorsed in STRIDE II, monitoring other targets could also be useful and improve cost-effectiveness (Table ~~4~~5). Cross-sectional imaging provides data on the intestine beyond the reach or view of endoscopy in Crohn's ~~CD patients~~disease patients. However, both MRI and CT scanning are expensive and~~ and~~ limited, with CT being the greatest source of diagnostic medical radiation. Intestinal ultrasound is a rapid and cost-effective monitoring tool in centres with the necessary equipment and expertise. In ulcerative colitis~~UC~~ patients, there is additional benefit in monitoring histology over and above endoscopy and, where therapeutic options allow, escalating treatment to normalise histology should be considered (and is the subject of ongoing randomized studies, e.g., NCT04259138). In the future, PROM and inflammatory biomarker combinations, biomarker–TDM (therapeutic drug monitoring) combinations, or new biomarkers discovered through multi-'omics' profiling are likely to surpass the accuracy of FC and other single biomarkers.[158–162] However, currently the cost of multi-'omics' profiling is prohibitive, even if there were strong data to support its use.

#### 4.4.5 Treatment Optimisation

Monitoring in IBD is useful to determine both disease activity as a therapeutic target and drug concentration as a determinant of dose adequacy and drug pharmacokinetics. Thiopurine drug monitoring has been used to confirm adherence and understand inter-individual differences in drug metabolism that could lead to therapeutic strategies for improving efficacy.[163] However, TDM can be used either reactively or proactively to optimise anti-TNF drug dose or ensure timely switching within or between classes of biologics. Reactive TDM refers to its use at the time of clinical manifestations, such as treatment failure or suspected toxicity. Proactive TDM refers to routine monitoring of drug concentrations at pre-defined time points, irrespective of whether the patient is in remission or has active disease. Anti-drug antibodies (ADAs) are a common cause of therapeutic failure and are measured as part of TDM, in addition to drug concentrations. Despite both the TAXIT (Trough Level Adapted Infliximab Treatment) and TAILORIX (Tailored treatment with infliximab for active Crohn's disease~~CD~~) studies failing to demonstrate a benefit to proactive TDM,[164] numerous retrospective studies have suggested that proactive TDM and measuring anti-drug antibody concentrations can guide decisions about anti-TNF withdrawal or restarting after a drug holiday.[165–172]

In 2017, a systematic review concluded that reactive TDM strategies lead to major cost savings in anti-TNF therapy (in both IBD and rheumatoid arthritis patients), with no negative impact on efficacy.[173] The modelling studies used have recently been reviewed by Yao *et al*. who found the overall quality to be moderate-to-high, although they did note the absence of productivity cost assessments.[139] The conclusion of both reviews was that TDM of infliximab was cost-effective. However, these studies are limited by the fact that the low TDM/antibody probabilities reported in real-world cohorts vary significantly; these models are based on soft data and have very wide confidence intervals.

The most recent cost-effectiveness analysis (published in 2021) — including RCTs, pharmacoeconomic and observational studies — concluded that reactive TDM of infliximab

optimises dosing and reduces expenditure by over 50%, without affecting clinical outcomes.[169,170,174–178] It also concluded that proactive infliximab TDM may confer long-term clinical benefits, but is only modestly cost-effective.[179] Recent randomised Norwegian studies have addressed the proactive TDM-based approach to infliximab dosing across a range of inflammatory indications, including IBD. These studies showed that proactive TDM was no better at inducing clinical remission in patients newly prescribed infliximab. However, a proactive TDM approach was found to be significantly more effective than standard care during the maintenance phase of infliximab treatment.[180,181] No cost-effectiveness analysis was made in these studies.

The cost-effectiveness of anti-TNF TDM is difficult to prove at a societal level. There may be direct cost reductions where anti-TNF is discontinued due to lack of response despite high drug levels, or low drug levels with antibody formation.[182] However, the cost for newer biologics and small molecules for patients with failing anti-TNF drugs is high. Future studies of treatment decisions based on inflammatory biomarkers and drug concentrations are needed that measure both direct and indirect costs. Without such studies it is difficult to understand the benefits of monitoring targets as part of treatment. Further studies are needed to understand the cost-effectiveness of TDM for thiopurines and biologics other than infliximab (including adalimumab, vedolizumab, and ustekinumab) and whether its cost-effectiveness is altered by using biosimilars.[179]

# 5. How Can We Deliver Affordable IBD Care in High-Income Countries?

## 5.1 Cost-saving Measures

When choosing therapy for patients with IBD, some of the most important considerations are effectiveness, safety, patient preference and cost. With the advent of biological and oral small molecule therapies a further important consideration is route of administration. While these parameters are used to formulate therapeutic decisions, ultimately every health care provider is limited by the local availability of therapies, which is itself driven by costs.

Prior to the advent of biological drugs, thiopurines and methotrexate were the mainstay of immunomodulating therapies. Corticosteroids, which are inexpensive worldwide, have continued to be used to induce remission in moderate-to-severely ill patients and there is evidence that thiopurines and methotrexate are effective at maintaining remission.[183] Even though studies such as SONIC and SUCCESS have proven that an anti-TNF plus thiopurine is superior to a thiopurine alone in managing Crohn's ~~CD and~~disease and ulcerative colitis~~UC~~,[184,185] many patients respond well to thiopurines, which are considerably cheaper than biological therapy[186]. In industrialized countries a dichotomy has emerged whereby thiopurines continue to be a mainstay of IBD therapy in Europe and Australasia, but are increasingly considered only an adjunctive therapy in North America.[187]

The use of combination therapy with thiopurines or methotrexate increases the cost of biological therapy, but at least with anti-TNF therapy this is offset by improved outcomes that lead to enhanced health-related quality of life and a reduction in other expenditures, such as for hospitalizations and surgeries.[184,185] Determining the exact cost savings by choosing one therapy over another highly dependent on local costs. Surgeries are much less costly in Canada than in the US, for instance, while biological therapy may be similarly priced in both countries. Hence, anti-TNF therapy does not reduce direct costs even if it reduces the strain on health care resources[22]. If surgeries are less costly, then a well-timed surgery may be more cost-effective in select scenarios, such as Crohn's ~~CD limited~~disease limited to a short segment of the terminal ileum[188]. In a Canadian population-based study, infliximab therapy was not found to reduce hospitalization and surgery rates in cases of Crohn's ~~CD or~~disease or UC. The authors speculate that the failure to demonstrate reductions was potentially related to misguided use of infliximab in patients with Crohn's ~~CD and~~disease and an underuse of infliximab in patients with UC.[189]

While biological therapies have been revolutionary in our management of IBD, they have driven costs up exponentially.[21,25,190,191] There are two main approaches that have emerged to mitigate these costs. The first has been the introduction of biosimilars. These compounds have proven to be comparably effective to their originator molecules.[192] The biosimilar industry has put downward pressure on the costs of biological therapies. In Canada, the ten provincial governments that oversee the health insurance provider programs have mandated initiating biological therapy with biosimilars rather than the originator compounds. Mandatory switching to biosimilars is now common in Europe as well. In some places a mandatory switch from an originator to a biosimilar compound for long-term users of biologics has been instituted.[193] With drugs of the same class being offered either subcutaneously or intravenously, there is some evidence that subcutaneous administration may be less expensive according to one analysis of direct/indirect costs that excluded acquisition costs.[194] However, adherence might fall with subcutaneous, rather than intravenous, therapies and the impact of non-adherence on costs has yet to be determined.

A second approach to reducing costs has been to de-escalate therapy when deep remission has been achieved, using regular patient monitoring for disease activity through serology, endoscopy, and radiology. While the precise timing of measuring drug levels and the optimal dosing of certain drugs continue to be debated, it is clear that drug level and antibody measurements can be useful

for guiding drug dosing and can improve cost-effectiveness.[139] For instance, a person in deep remission, that is to say with no symptoms and with a normal serum haemoglobin, normal CRP, normal serum albumin, and a normal ileocolonoscopy, who has been on weekly adalimumab for five years, might be de-escalated to therapy every other week. Recently, data from the Lengthening adalimumab dosing interval in quiescent Crohn's disease patients (LADI) study, reported that increasing adalimumab dosing interval from two to up to four weeks in quiescent Crohn's disease patients was non-inferior in terms of persistent flares (>8 weeks duration) and led to lower use of the drug.[195] However, clinical remission rates at the end of the study were lower in the control group continuing treatment every other week indicating that this approach might only be relevant in a subset of patients. Outright discontinuation of a biological therapy might also be considered, but current controlled trials assessing discontinuation have failed, partly because they withdrew treatment too early on in the course of therapy.[196–198] In terms of discontinuation of the immunomodulator when combination therapy is proving successful, a systematic review did not arrive at a firm conclusion as to the merit of this approach.[199]

Another potential source for cost-savings is the use of intestinal ultrasound for the diagnosis and monitoring of IBD.[200,201] Intestinal ultrasound has high accuracy, sensitivity, and specificity compared with other modalities, such as MR and CT, in both Crohn's ~~CD and~~disease and ulcerative colitis~~UC~~ patients[202,203] and is non-invasive, unlike endoscopy. Intestinal ultrasound has been shown to reduce the need for additional endoscopy and MRI and, thereby, costs when used as a regular tool for disease monitoring[204].

## 5.2 Environmental Risk Factor Modification: Reducing Incidence and Disease Severity

Since the turn of the twenty-first century, the incidence of IBD has begun to stabilize, and in some regions fall, in the Western world. In contrast, newly industrialized countries in Asia, Africa and Latin America are observing rapidly rising incidence rates of IBD.[34] The primary driver of the changing incidence of IBD throughout the world are modifications of the environmental determinants of IBD.[205] Numerous studies have explored the impact of environmental risk factors on the risk of developing IBD. For example, smoking is associated with an increased risk of Crohn's disease~~CD~~, whereas quitting smoking is associated with a higher risk of ulcerative colitis~~UC~~. Early exposure to antibiotics increases the risk of developing IBD, whereas breastfeeding protects against IBD. Diet has a profound effect on IBD risk, with Western diets associated with refined sugars and highly processed food contributing to the onset of IBD. Consequently, environmental risk modification strategies at a population level, or targeting individuals at high risk of developing IBD (e.g., first-degree relatives), offer the potential to prevent IBD and reduce incidence over time.[8,206]

Environmental risk factor modification is a strategy to reduce the cost of IBD care for those with established disease.[207] Diet and lifestyle factors (e.g., smoking) are associated with worsening symptoms and disease course. For example, individuals who continue to smoke following a diagnosis of Crohn's disease~~CD~~ are at higher risk of early surgical intervention and postoperative recurrence. In contrast, smoking cessation following the diagnosis of Crohn's disease~~CD~~ is associated with improved disease course, including a reduced risk of flare-ups or of requiring escalation of medical or surgical management. A cost-effectiveness analysis demonstrated that a smoking cessation program targeting those with Crohn's disease~~CD~~ saved millions of health care dollars within the first five years of patients quitting smoking, as well as significant downstream health savings from smoking-related complications such as cardiovascular disease and cancer.[208]

## 5.3 Dissemination, Implementation, and Quality Improvement for Increasing Care Reliability

### 5.3.1 American Models

In the United States, health care costs associated with IBD ~~are~~ in 2016 were estimated to be $~~7~~25·~~24~~ billion/year, a substantial portion of which originated in ED costs and hospitalizations.[209] However, much of this expenditure could be avoidable. It stands to reason that improving access, reliability, and quality of care through low-cost process changes may advance the triple aims of health care: improving patient experience and health outcomes while reducing per capita costs.

A 2014 retrospective chart review of seven paediatric IBD centres demonstrated that approximately 20% of ED visits were medically unnecessary and 50% were considered avoidable if the health system were more responsive and better coordinated.[210] In response to this opportunity, a number of initiatives have recently been established with the broad goal of optimizing outpatient IBD care in an effort to reduce unplanned emergency department visits and hospitalizations. The ImproveCareNow Paediatric IBD network was created to improve the reliability and quality of chronic illness care and its results over the last decade indicate sustained improvements in remission.[211]

In parallel, an adult IBD learning health system, IBD Qorus, a national quality improvement program in partnership with patients' associations, has been developed that emphasizes the patient-physician relationship. It has used a Breakthrough Series (BTS) Collaborative approach to quality improvement (QI) to enhance the delivery of outpatient IBD urgent care.[212] The initiative tested 19 ideas for change over 15 months at 24 centres across the US and observed modest decreases in ED use (18% to 14%) and hospitalization (14% to 11%). Based on a Markov decision model, participation in the urgent care intervention decreased costs by $2,949/year per patient when compared to the baseline.

Another recent innovation is the IBD Specialty Medical Home (SMH), pioneered by the University of Pittsburgh. In the SMH, coordinated care is provided by a multidisciplinary team comprising a social worker, dietitian, schedulers, nurse coordinators, and advanced practice providers, and it is led by a gastroenterologist and a psychiatrist. This model resulted in a 47·3% reduction in ED visits, a 35·9% reduction in hospitalizations and better quality of life.[50] Subsequently, Project Sonar has expanded this model to the private practice setting and incorporates 1) an EMR-embedded set of decision support tools based on published care pathways, 2) a risk assessment tool, 3) a technology-enhanced patient engagement platform, and 4) regular use of commercial claims data to analyse the impact of the program. Initial results from a single centre suggest reductions in unplanned hospitalizations and ED use, and the project is soon to be introduced at dozens of additional practices.[213]

### 5.3.2 British Model

In an effort to improve the overall quality, reliability and safety of care for IBD patients in the UK, a national audit, in addition to quality improvement initiatives, was begun in 2014 and is planned to run for 12 years.[214] The objectives of the programme are to assess the structure and organisation of care and the processes and outcomes of care delivery. It also aims to allow hospitals to assess their service delivery against national standards and to facilitate a process for improving the quality of care. Data are being captured on inpatient care, inpatient experiences, primary care services, the service structure, and biological therapies, and has evolved from retrospective to prospective data collection.

The results of the initial audit prompted the development of the national IBD Standards document in 2009, which was updated in 2013 and 2019.[215,216] Subsequent audit rounds enabled hospitals to see how their services compared with national standards and with other hospitals. This feedback helped individual hospitals improve key aspects of their service and the programme was able to guide quality improvement initiatives, including national-level plans, workshops with defined projects, and the

sharing of best practices. Improvements in quality of IBD care that were noted and measured by the national audit included a decrease in adult mortality during admission from 1·54% in 2008 to 0·75% in 2014, an increase in the number of hospitals with an IBD nurse (from 56% to 86%), an increase in the number of sites with a dedicated gastroenterology ward, a decrease in time from diagnosis to initial treatment with biologics, and a reduction in the frequency of surgery prior to biological therapy.

Rates of participation in the audit process increased from around 76% in the first audit round to more than 95% by the end of the process. How was this achieved? What were the levers? Each hospital had a 'lead clinician' to take responsibility and the Chief Executive of the hospital was kept informed of the process. The teams were engaged throughout the process with regular feedback, and involvement of the national charity and gastroenterology society ensured widespread dissemination of its results. The programme initially received funding from the Health Foundation, followed later by NHS funding of around £2 million over the 12-year project, equating to around £115 per patient in the audit. The initiative has been adopted by other countries such as the Netherlands, Australia, and New Zealand.

While further work is needed to refine and disseminate the interventions and determine whether the improvements in outcomes and cost savings are sustainable in the long-term, these early initiatives provide a proof of concept that using QI and implementation science can yield improved care at a lower cost.

## 5.4 Patient-centred Care in IBD

### 5.4.1 Education and Empowerment

Education is of paramount importance for ensuring the optimal allocation of resources. This is true for both patients and physicians. The physician-patient relationship is integral to the decision-making process. Doctors should be trained to review evidence of treatment modalities and new techniques, and they should be aware of the cost of each treatment plan and alternative strategies. Knowledge of the cost-effectiveness of each treatment plan is essential for ensuring effective and affordable care. Patients should also recognize that adherence is one of the key factors in a treatment's success. Moreover, to ensure informed decision-making patients need access to both clinical and cost information about their treatment options. While the use of biologics has set new targets in disease management and has transformed IBD care, patients and physicians may have different hierarchies of needs. Patients must be educated about the merits and potential adverse effects of treatments, but also the importance of treatment monitoring and adherence. Physicians must also learn what their patients want and what their patients are prepared to do to achieve it. Treatments used inappropriately will be even less cost-effective. While patient education leads to patient empowerment, and patient empowerment and shared decision-making has gained popularity in clinical practice, the extent to which patients wish to be involved in selecting treatment varies greatly.[217]

### 5.4.2 Coordinated Care

An evidence-based care pathway can help to optimize care choices. Disease monitoring is crucial and has evolved with the growth of telemedicine during the COVID-19 pandemic. However, the positive effects of home-based care have been apparent since the early 2010s in patients with ulcerative colitis~~UC~~. In a randomised controlled trial in Denmark and Ireland, patients with ulcerative colitis~~UC~~ were randomised to web-based education and self-treatment or continuing with their usual care for 12 months. The number of acute and routine visits to the outpatient clinic was lower in the web-based group than in the control group, resulting in a saving of €189 per patient per year. Home-based care also empowers patients with ulcerative colitis~~UC~~ without increasing their physical or mental health morbidity.[86,218] In one Dutch study, telemedicine resulted in lower mean annual costs of €547/patient (95% CI, €-1,029-2,143). This translated to an increased incremental cost-effectiveness over standard care in 83% of replications and an incremental net monetary benefit of

€707/patient (95% CI, €1,241-2,544).[84] In a Spanish study, a web-based platform showed promise as being more cost-effective than standard and telephone care.[219]

A separate study using electronic health screening showed equal efficacy in using scheduled interventions or on-demand monitoring in patients with ulcerative colitis~~UC~~.[220] Self-management with home-monitoring of disease activity has been shown to result in significantly faster remission compared to standard care.[220] Similarly, personalized, multidisciplinary care plans are necessary because of the chronic nature of IBD, the typically young age of the affected population, the complications and multiple interventions that occur, and the extraintestinal organ systems that can be affected. The in-house IBD mobile app developed by the Leuven group, with full integration within the electronic medical records, enabled continuous remote monitoring and allowed for the accurate detection of flare-ups.[220] Overall, telemedicine systems are safe and feasible for the management of IBD and are met with high acceptance from patients. Information and communication technologies can be used to enhance medication adherence, empowering patients to control their disease and optimize drugs during times of active disease, which can lead to fewer outpatient visits and less time away from school and work.

## 5.5 IBD Nurses

The care for IBD patients should ideally be provided by a dedicated, multidisciplinary team including physicians, nurses, dieticians, surgeons, psychologists, pathologists, and social workers. The role of the IBD nurse in access to education, advice, and support is central in this team. Specialized IBD nurses contribute to the care of IBD patients in many ways. Coenen *et al*. prospectively recorded all nurse-patient contacts in the first year after introducing an IBD nurse in their tertiary IBD practice and correlated more than 1,300 contacts with outcomes.[221] The IBD nurse provided counselling at the start of new therapy or during follow-up, provided information about the disease, helped with managing flare-ups, provided psychosocial support, and assisted with questions about side effects. Having an IBD nurse in place provided faster access to procedures and other departments for some patients. The most important finding was that the IBD nurse position resulted in a decrease in emergency room visits and unscheduled outpatient visits, hence reducing direct costs.[221,222] The value of IBD nurses as the first point of contact and counselling is obvious, although their cost-savings may also be associated with these contacts.

A nationwide study in Finland demonstrated the impact of an IBD nurse on the quality of care and on budget savings. Clinics with an IBD nurse reported fewer patient hospitalizations (4-9% vs. 11-19%, $p$ <0·001) and resulted in reallocating physicians' time.[223] In this way the estimated annual cost savings of having an IBD nurse may be significant and should be further mapped. A retrospective cohort study from Australia demonstrated the economic impact of implementing a nurse-led IBD advice-line and virtual clinic, which led to an annual net benefit of $11,663 AUD.[224] Furthermore, data from a district general hospital in the UK showed that a nurse-led telephone advice line was a cost-effective intervention by preventing unnecessary emergency or hospital visits, and appointments with general practitioners or consultants.[225]

It is becoming more apparent that including an IBD nurse in an IBD team is cost-effective.[226] So why then do not all IBD centres have IBD nurses? A survey among IBD nurses and nursing services across Canada showed large differences in training and diplomas (53·8% were diploma-prepared registered nurses, 35·3% Baccalaureate-prepared nurses, and 4·4% Master's-prepared nurses) and also large regional differences.[227] There might also be a maldistribution of the practice locations of IBD nurses; in the same survey almost half of all nurses were employed in Ontario, followed by 20% in the province of Alberta and 9% in British Columbia. Many nurses, although working with IBD patients, also held multiple roles and responsibilities, and provided a variety of services. Further studies evaluating IBD nurses' scope of practice, regional differences in the provision of IBD nursing

care, and barriers and enablers of access to IBD nurse positions within and between countries are required.

## 5.6 Future Directions

Measures to reduce the costs of IBD care are summarised in Table ~~6~~5 as well as suggestions as how to implement these measures. Increases in health care costs must be evaluated against improved disease control and reductions in indirect costs. Evaluations should be systematically aligned between countries and regions (e.g., using systems such as NICE or ICER). Detailed analysis of the current epidemiology and the likely effects of changing IBD management on disease course and socioeconomic outcomes is essential; this will become even more imperative in the era of precision medicine, where complex biotechnologies will require expensive analyses, highly skilled personnel, and drug development for what may sometimes be relatively small patient groups.

New therapies, treatment algorithms, and care models will continue to be developed; thus, establishing overarching systems for data interoperability, registries, and big data approaches for continuous assessment of the costs and cost-effectiveness of care is essential. There is a need for global collaboration and international IBD consortia-driven efforts that focus on ~~:~~

e~~E~~stablishing and consolidating epidemiological research platforms (e.g., combining comprehensive clinical data with data from national health and social security registries) to estimate short- and long-term socioeconomic outcomes, including health care usage by patients and society, and ~~.~~evaluate incidence, with carefully curated health-care utilization and cost data.

Developing models that facilitate economic evaluations in targeted treatment as well as comparative effectiveness studies of the different medical and surgical interventions to help inform value-based decision-making ~~and precision medicine~~could~~,~~ ultimately lead~~ing~~ to more sustainable and more effective treatments, as well as cost-effective clinical trials. This requires efforts to facilitate IBD data interoperability, to help perform comparative effectiveness research studies for more accurate comparisons of outcomes.

Precision medicine is currently being applied to IBD via treat-to-target goals, therapeutic drug monitoring, stratification via serologic response to antimicrobial antigens, and genetic data (TPMT and NUDT15).[4] However, development of increasingly sophisticated decision support tools to make phenotypic and prognostic recommendations based on patient findings (genetic profile, protein expression at the tissue level, and microbial signature) is currently underway and represents an important component of precision medicine.[228] Precision medicine is also being applied to the delivery of targeted therapies based on complex and proactive dashboard modelling that includes pharmacogenomic and other patient-specific factors—instead of trial and error—to reduce exposure to ineffective medicine and avoid toxicity, as well as toobtain response and remission faster, reducing compications and costs.[229] Although expected to drive significant costs, there are efficiencies and economies in attaining precision that could potentially offset such costs in the future.

- ~~Comparative effectiveness studies of the different medical and surgical interventions to help inform value-based decision-making.~~
- ~~Epidemiological studies evaluating incidence, with carefully curated HCU and cost data.~~
- ~~IBD data interoperability, to help perform CER studies for more accurate comparisons of outcomes.~~
- ~~Payment reform and studies evaluating novel models of care, including VBHC.~~

Demonstrating that costs are also driven by the quality of IBD care allows for an opportunity to further define potential low-value patterns of practice and standardize quality indicators to ensure more appropriate, better-value care. For a sustainable IBD health care infrastructure, high-income countries have a responsibility to assess the efficiency of health care delivery in IBD and to use this

evidence to support the highest-value interventions and care. Transnational non-profit organizations (such as the European Crohn's and Colitis Organisation and International Organization for the Study of Inflammatory Bowel Disease), in collaboration with patient organizations, should take responsibility for establishing optimal strategies for implementing international guidelines and supporting country-specific implementation of the most efficient care models.

This should be done by:

Aassessing the barriers to implementing guidelines;
dDeveloping more strategies to improve the appropriateness and efficiency of care; e.
Pperforming studies that evaluate novel models of care (such as value-based health care, including integrated health care and participatory health care models); and
Ffinding new approaches to improving quality through the education and training of clinicians, patients, and policy makers.

In this way, aligning IBD expertise can more uniformly and systematically bring about a harmonized globalization of IBD care, where the cost-effectiveness of new approaches can be evaluated based on consensus.

While this Commission has focused on the situation in high-income countries, confronting the challenge of increasing costs of IBD care will also be of great importance in the low- and middle-income regions of Asia, Africa, and South America. In these regions, the incidence and prevalence rates of IBD are set to increase rapidly in the coming years, which they will need to tackle despite having severely limited resources. This necessitates high-quality economic evaluations, service delivery interventions, and evidence supporting the optimal configuration of services in high-income countries, from which most of our current data originate.

# 6. SUMMARY

Estimating the true costs of IBD within a region, or comparing costs between regions/countries, can be difficult due to the vast heterogeneity of health care systems and a lack of transparency in how prices for medications and services are set across the world. However, the increasing financial burden of IBD on health care systems has been reported from practically all regions of the industrialized world.

Cost increases have primarily been driven by the introduction of new and costly treatments, together with ever more intensive and expensive disease monitoring and treatment paradigms that use more frequent testing and that start treatment with costly agents earlier and more often. But other important factors at a societal and structural level also contribute to rising costs, including inequality in access to care and a lack of means to optimize patient involvement and adherence. Continuous education and subspecialisation of the gastroenterologist is paramount for the cost-effective diagnosis, treatment and follow-up of IBD patients.

As the prevalence of IBD continues to increase, so will its costs. In view of the inevitable increase in spending on IBD management, some key questions remain: 1) Will the anticipated increase in spending on novel therapies be offset by improved patient outcomes and reductions in disease burden? 2) What effect will the emergence of more stringent treatment targets and earlier, more aggressive treatment have on per-capita spending on IBD? 3) What cost savings can we expect from the greater uptake of cheaper alternatives such as biosimilars and the adoption of digital health tools?

This Commission has identified some key areas in which progress is needed at the national and international levels. First, the responsibility of countering increasing costs lies, in part, with the treating physicians and with the research community. Both need accurate cost-effectiveness studies of current treatments and strategies, which are currently lacking. They should urgently be undertaken to serve as platforms for assessing the efficiency of health care delivery and for informing providers of where costs arise.

Other initiatives to battle increasing costs must come from governments or payer/health care systems. The aim should be to improve access to care, and its reliability and quality, including supporting implementation of new models that make use of value-based care concepts. These solutions should ideally be informed by large data sets from patients in real-world care settings, with feedback loops for continuous quality improvement. In these ways, we believe that high-value and affordable IBD care can be provided without detracting from treatment quality, and that the management tools, evidence, and methods used to achieve this care can be made available to affect a transformation across all developed countries.

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## 8. FIGURE LEGENDS

Figure 1. Drivers of direct and indirect costs of inflammatory bowel disease.

Figure 2. Annual distribution of costs for patients with Crohn's disease and ulcerative colitis in a European inception cohort (from Burisch *et al.*[11]).

Figure 3. Inequality in access to inflammatory bowel disease care.

Dear Editor, dear Rob,

Thank you for these constructive comments and suggestions.
We have addressed the comments below and have made changes to the manuscript and tables in accordance with them.

Best wishes,
Johan

**Responses to reviewers**

1. Response to reviewer 1, comment 2 - "The authors try to give concrete examples of cost and quality initiatives or cost effectiveness studies with sometimes reviewing the methodology in a lot of detail but the choice of highlighted works seems at times random when other works are not mentioned or only extremely briefly." - you have not responded to this point in your rebuttal letter.

Response: We acknowledge the opinion of the reviewer. Throughout the work on this report, member of the commission reviewed and discussed the available literature but – except for the searches for available cost-effectiveness studies as well as cohorts reporting on direct and indirect costs – without the aim of systematically reviewing all available studies. If the reviewer knows of specific studies that were overlooked or discussed with too little detail, we'd be happy to consider including them.

2. Response to reviewer 1, comment 3 - it is unclear where you have made this change - please quote the specific section.

Response: Apologies, we had added the sentence "However, most patients were not treated with biologics…" to the section after mentioning mean costs for biologics; second paragraph of "Europe", supplementary file page 1.

3. Response to reviewer 1, comment 5 - it is also unclear what change you have made to discuss how much an increase in cost is an increase over inflation, rather than just the increase itself. Please clarify.

Response: As we did not find any studies discussing this topic, we added a sente to the summary of section 2.2 stating "Furthermore, studies taking inflation and its impact on increasing costs over time into consideration are missing" to state that his a topic that needs more data.

4. Response to reviewer 1, comment 14 re precision medicine - is this perhaps something that might be worth mentioning in future avenues of research?

Response: Thank you for that suggestion, we've added parts of the deleted paragraph to the future directions.

5. Response to reviewer 4, comment 4 - table 6 needs another column to indicate how introducing each of the measures might be brought about (and by whom), in addition to how it could subsequently be measured. See also editorial comment 22.

Response: We have substantially changed table 6 (now table 5) and have added suggestions on what to do and how to measure

**Specific Editors' comments**

1. You acknowledge the Helmsley trust in your acknowledgments section. Please specify what their contribution was.
Response: We have added information on their contribution to the manuscript. Figures were drawn by personnel and software made possible through Grant number G-2108-04777. If this is inappropriate, we will of course be happy to remove it.

2. Please remove the keywords; our systems do not use them and we do not publish them.

Response: They have been removed.

3. Throughout - please spell out Crohn's disease and ulcerative colitis, rather than abbreviate them.

Response: done

4. Please avoid the use of the word "sufferer", "suffering", etc - we avoid such terms to describe individuals living with a chronic illness.

Response: we have rephrased these parts of the manuscript.

5. Page 11 - "Medication costs have increased tremendously..." - please add a reference to this sentence.

Response: We've changed the wording slightly to make it clear that the whole statement refers to reference no 21.

6. Page 11 - paragraph that starts "What follows is a review of representative..." - this seems also to describe the indirect cost studies too, so please add that to the first sentence.

Response: added

7. Page 11 - same paragraph - you state that no attempt has been made to synthesise the studies identified, but then go on to present an estimate of costs; please revise accordingly.

Response: thank you making us aware of this inconsistency. We have revised the section (now placed in the supplementary file) accordingly.

8. Please move the long sections summarising the studies you found for both direct and indirect costs to the appendix, together with table 2; they can be replaced in the main text with a couple of paragraphs introducing them, but explaining that little can be synthesised from them. Our experience shows that long sections like this is where readers stop paying attention, so moving them to the appendix will help focus the report and the reader.

Response: We have moved the summaries of available cohorts as well as the table to the supplement as suggested.

9. Section 2.2.3 - this section includes examples that are not from high-income countries, and are thus outside the scope of the Commission. Please remove these examples.

Response: They have been removed from the section, which is now placed in the supplementary file.

10. Page 14 - what do you mean by "Pareto subgroup"? This isn't referred to anywhere else in the manuscript.

Response: We've rephrased the part to make it clear that these 28% of patients (the Pareto subgroup) accounted for 80% of costs. This part has been moved to the supplementary file according to previous comments.

11. Section 2.2.5 - you introduce this paragraph with "Our estimate", without having first explained that you were attempting to come to an estimate, nor how. It might be better to start this section with the estimate and how you arrived at it, before discussing the problems faced in reaching this estimate.

Response: We agree and have changed the section accordingly.

12. Section 2.3.4 - Brazil is a high-income setting; please remove.

Response: we have removed the section

13. Section 2.4.3 - Is there any evidence that competitor originator drugs will drive down the costs of pharmaceuticals?

Response: We have revised the sentence slightly and added references.

14. Section 3.1 - "As outlined in section 2" - this point itself is not made in section 2, please just start the sentence with "The most certain way" (perhaps better as "The most obvious way"?). The sentence starting "In brief,..." can be deleted as it it doesn't need stating. Perhaps start the sentence "In the absence of proven..." as "However, in the absence of proven...".

Response: done

15. Section 3.1.2 - "Similarly, areas where governments have restricted the number of gastroenterologists..." - please give example and reference.

Response: Unfortunately, the author of the specific section could not give a specific reference or example for this statement. It was based partly on theoretical discussions (for example: https://hbr.org/2014/11/how-not-to-cut-health-care-costs). We have therefore removed it from the manuscript.

16. Second Section 3.1.2 - Describing HNHC patients as a "drain on" resources might be felt pejorative, perhaps reword to "the high expenditure on HNHC patients"?

Response: We agree and have changed the wording.

17. Section on cost-effectiveness of different treatments - you don't seem to draw a conclusion from the studies you found cost-effectiveness for the different treatment modalities. Please add a brief summary. This summary can also highlight the lack of cost-effectiveness data for ustekinumab, tofacitinib, etc, as raised by reviewer 1.

Response: We have rephrased section 4.2.3. to summarize the findings as well as to address needs for future studies.

18. Page 33 - There seem to be words missing from the end of the sentence that begins "However, both MRI and CT scanning..."

Response: Apologies, but we cannot find this. The sentence in the manuscript is “However, both MRI and CT scanning are expensive and limited, with CT being the greatest source of diagnostic medical radiation”.

19. Page 35 - the LADI trial, presented at UEG, provides an example of lengthening intervals between doses of adalimumab for patients in remission; worth citing here?

Response: Thank you for this excellent suggestion. This has been added to the end of section 5.1.

20. Section 5.3.1 - the figure of $7.2 billion per year needs a reference.

Response: We have added a recent reference estimating costs to be 25.4 billion $.

21. Throughout, please convert bulleted lists in the text to prose.

Response: done

22. Table 6 - the measures listed under indirect costs do not seem to be measures, but rather outcomes. Please adjust as necessary.

Response: Thank you for this constructive comment, we have changed the table accordingly.

Figure 1

Click here to access/download;Figure;Figure 1.tif

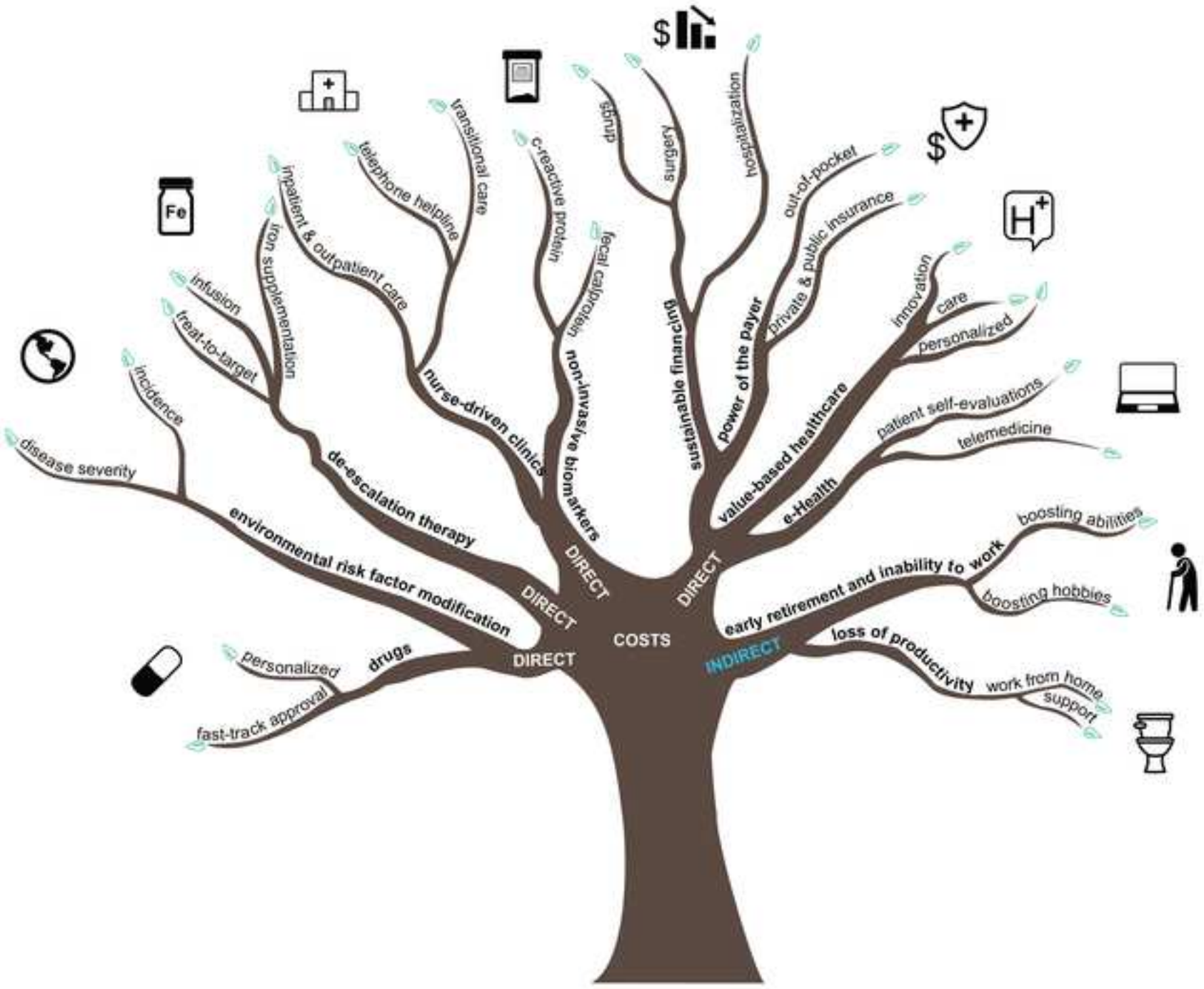

Figure 2



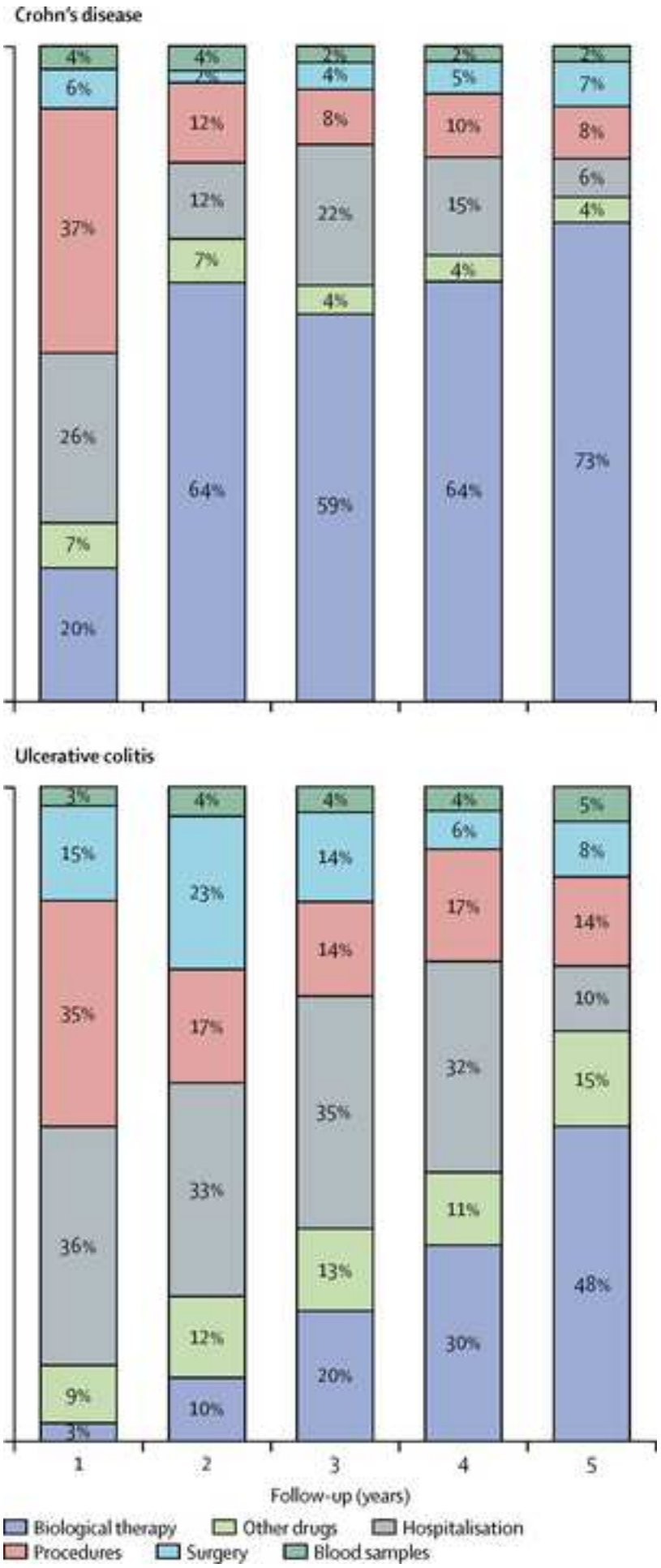

Figure 3



## TABLE 1. TARGETS FOR REDUCTION IN DIRECT AND INDIRECT COSTS IN IBD

| **Direct costs** |
|---|
| Drugs (biological and non-biologics, biosimilars) |
| Consultations (at diagnosis, at follow up, at post-discharge follow up emergency visits, prescription of drugs and laboratory tests) |
| Laboratory tests (blood, histology, radiology, endoscopy) |
| Hospitalization (including re-admissions & one-day clinic) |
| Surgery (including stoma and pouch care) |
| Prevention of IBD through environmental risk factor modification |
| **Indirect costs** |
| Absenteeism, including |
| sick leave |
| short- and long-term disability |
| early retirement |
| premature death |
| Presenteeism, indlucing |
| loss of productivity |
| loss or reduced education |
| Restriction of leisure time |

## TABLE 2. ANNUAL COST OF DRUGS 2020-2021 (CURRENCIES CONVERTED TO EUROS FOR DIRECT COMPARISON, BASED ON EXCHANGE RATES IN JULY 2021)

| | Country GDP, most recent (million $)[1] | Pentasa 2 gm/d | AZA 100 mg/d | 6MP50 mg/d | MTX 25 mg.wk | Adalimumab originator 40 mg EOW | Adalimumab biosimilar 40 mg EOW | Infliximab originator 400 mg q8wks | Infliximab biosimilar 400 mg q8wks | Vedolizumab 300 mg q8wk | Ustekinumab Every 8 weeks |
|---|---|---|---|---|---|---|---|---|---|---|---|
| #Australia June, 2021 | 1,542,660 | 605€ | 152€ | 437€ | 76€ | Year 1: 15,173€ | See footnote | Year1: 11,546€ | See footnote | Year1:16,880€ | Year 1: 39,391€ |
| | | | | | | Year 2: 14,636€ | | Year 2: 8,980€ | | Year2:13,129€ | Year 2: 34,619€ |
| *Belgium June, 2021 | 599,879 | 451€ | 159€ | 273€ | 1,148€ | 6,071€ | 5,909€ | 8,856€ | 8,856€ | 14,400€ | 11,710€ |
| ǂCanada July 2021 | 1,990,762 | 659€ | 283€ | 747€ | 245€ | 16,849€ | 9,869€ | 22,597€ | 11,345€ | 19,068€ | 20,469€ |
| &Croatia June, 2021 | 67,838 | 386€ | 128€ | N/A | 793€ | 7,607€ | 7,607€ | 8,614€ | 8,614€ | 8,613€ | 16,366€ |
| ##Czech Republic June, 21 | 282,341 | 323€ | 106€ | 1,034€ | 1.433€ | 7,117€ | 7,117€ | 8,068€ | 8,068€ | 13,620€ | 15,447€ |
| ***Denmark Fiscal 2021 | 397,104 | 738€ | 113€ | 2,627€ | 1,914€ | 15,350€ | 1,328€ | 16,087€ | 5,399€ | 16,288€ | 20,751€ |
| ###Greece Fiscal 2021 | 216,241 | 506€ | 149€ | Not available | 1,014€ | 8,631€ | 5,784€ | 9,632€ | 7,744€ | 1,593€ | 2,339€ |
| Hong Kong June, 2021 | 368,139 | 760€ | 56€ | 1,233€ | 30€ | 11,940€ | 5,080€ | 12,900€ | 5,950€ | 6,450€ | 10,480€ |
| Italy June, 2021 | 2,099,880 | 609€ | 218€ | 428€ | 1,468€ | 5,605€ | 1,005€ | 6,393€ | 1,755€ | 10,718€ | 12,312€ |
| Israel June, 2021 | 481,591 | 523€ | 117€ | 920€ | 115€ | 12,198€ | Not available | 17,820€ | 17,820€ | 19,985€ | 25,527€ |
| ǂǂJapan June, 2021 | 4,937,422 | 754€ | 598€ | 143€ | Not available | 10,920€ | 7,175€ | 12,712€ | 6,659€ | 12,585€ | 22,917€ |
| ǂǂNew Zealand June, 2021 | 249,992 | 480€ | 50€ | 317€ | 16€ | 12,222€ | Not available | 12,314€ | Not available | Not available | Not available |
| **Norway 2020-2022 | 482,437 | 591€ | 98€ | 327€ | 1,213€ | 1,403€ | 1,216€ | 3,092€ | 2,594€ | 16,700€ | 17,036€ |
| Spain June, 2021 | 1,425,277 | 368€ | 105€ | 60€ | 875€ | 13,404€ | 11,393€ | 13,300€ | 10,490€ | 22,598€ | 20,212€ |
| Switzerland | 812,867 | 741€ | 155€ | 1,150€ | 209€ | 15,658€ | 11,647€ | 16,461€ | 14,841€ | 16,209€ | 21,058€ |
| United Arab Emirates | 358,86 | 668€ | 116€ | 106€ | 55€ | 17,067€ | 11,953€ | 13,100€ | 8,504€ | 18,596€ | 19,552€ |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| June, 2021 | | | | | | | | | | | |
| ^United States | 22,996,100 | 6,463€ | 292€ | 2,019€ | 210€ | 39,000€ | Not available | 8,709€ | 8,709€ | 30,671€ | Not available |

The costs shown in Table 3 have been converted to euros based on exchange rates from July 2021

[1] Most current gross domestic product (GPD) (2020 or 2021) for countries as given by the World Bank (https://data.worldbank.org/)

*#Australia For infliximab/Adalimumab biosimilar negotiations are done between Pharma and Hospital pharmacies and large discounts are given*

**Belgium: For Adalimumab originator loading doses week 0+2 160/80 need to be given for free by the company. The price listed is for year 2 and beyond*
*For Adalimumab biosimilar loading doses week 0+2 160/80 need to be given for free by the company. The price listed is for year 2 and beyond*
*For infliximab originator negotiations are done between Pharma and Hospital pharmacies and large discounts are given*
*For infliximab biosimilar negotiations are done between Pharma and Hospital pharmacies and large discounts are given*
*For Entyvio negotiations are done between Pharma and Hospital pharmacies and large discounts are given*
*For ustekinumab in the first year, the IV and week 8+16 are given for FREE – the price listed is for year 2 and beyond year 2*

**ǂ***Canada: Data source is from Rxfiles*

*&Croatia: All prices are given by Croatian National Insurance Fund. Prices are based on negotiation between pharma and the NIF using the standardized methods of comparison with prices in several European Countries of similar GDP.*
*In the 1st year for all biologics (including biosimilars) loading doses (induction) up to week 16 need to be given for free by the drug company. At the end "pay- back" of money as a part of agreement with industry, connected with a volume of prescribed drugs.*

*##Czech Republic – annual costs calculated using data on maximum reimbursement of the health insurance company for each preparation; data obtained from the Czech ministry of health; the annual cost calculated using the current prices; cost of biological therapy provided for the 1st year of treatment (including induction doses)*

**** Denmark: Procurement and tendering procedures for biological therapies and small molecules are performed on a national level by a central institution that negotiates directly with pharmaceutical companies.*

*##Greece: All these prices are market prices, usually hospital prices are 10-15% cheaper from those listed in the table. Prices are calculated and negotiated between pharma and the Ministry of Health within the range (usually the median) of the 3 lowest prices of the same drug in 3 other European countries.*
*Data source for Greece prices is Galinos https://www.galinos.gr/*

**ǂǂ***Japan: All prices are market prices. The government subsidize costs, the extent of which is dependent on patients' income. Patients treated with biologics pay only 226-2709 Euro per year, and most patients less than 600 Euro per year. Patients using Pentasa only, pay 226 Euro per year.*

**ǂǂ***New Zealand: In New Zealand Pharmac is the national drug purchaser. Whilst the list cost is shown, large confidential rebates are negotiated to reduce the cost of pharmaceuticals to Pharmac.*

***Norway Cost of Asacol at 2.4 gm per day for one year is 912 Eur. For ustekinumab, the majority of users get ustekinumab more frequently than every 8 weeks.*

^United States: US data for Pentasa, azathioprine, 6MP, MTX, and adalimumab based on 2009 spending based on Medicare Part D Drug Spending and Utilization. This does not take into account commercial insurance. https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Information-on-Prescription-Drugs/MedicarePartD.
US data for infliximab originator, biosimilar, and vedolizumab based on 2021 Medicare Part B allowance. This assumes 8-week dosing. This does not take into account infusion related costs. This also does not consider commercial insurance. https://www.cms.gov/medicare/medicare-part-b-drug-average-sales-price/2021-asp-drug-pricing-files

Table 3

## TABLE 3. COST-EFFECTIVENESS ANALYSES IN INFLAMMATORY BOWEL DISEASE

| Author and publication year | Analysis | Conclusion |
|---|---|---|
| **Immunosuppressive treatment** | | |
| Mlcoch 2021[147] | Methotrexate | Parenteral methotrexate proved to be cost-effective in patients with mild-to-moderate CD. |
| Vasudevan 2020[148] | Immunomodulators or infliximab for CD in the biosimilar era | In the biosimilar era, initial azathioprine with escalation to infliximab appeared more cost-effective in the short term compared with infliximab or combination therapy, although initial combination therapy yields acceptable ICERs in the long term with continued reductions in anti-TNF therapy costs and will likely be the preferred treatment strategy in the future. |
| Vasudevan 2019[149] | Optimizing immunomodulators | Both thiopurine methyltransferase (TPMT) testing before commencing thiopurines and thiopurine metabolite testing for dose optimization seem cost-effective. |
| **Biologic treatment** | | |
| Bodger 2009[150] | Biological therapies for CD | The model suggests acceptable ICERs for biological agents when considering a lifetime horizon with periods of up to 4 years continuous therapy. |
| Bodger 2011[151] | Treatments for IBD | In CD, cost-utility models for anti-TNF drugs versus standard care have suggested consistently that incremental benefits are achieved at increased overall cost. However, studies of varying design have produced a wide spectrum of incremental cost-effectiveness ratio estimates. |
| Di Sabatino 2011[246] | Biological therapies for IBD | The use of anti-TNF agents may be a cost-effective approach in IBD patients, particularly for inducing clinical remission, although there are insufficient data for establishing the ideal duration of the treatment. |
| Marchetti 2014[247] | Biological therapies for CD | As clinical practice is moving to mucosal healing as a robust response marker, personalized schedules of anti-TNF therapies might prove cost-effective even in the perspective of the health-care system in the near future. |
| Pillai 2017[152] | Conventional vs biological vs surgical interventions for IBD | While biologic agents helped improve outcomes, they incurred high costs and therefore were not cost-effective, particularly for use as maintenance therapy. The cost-effectiveness of biologic agents may improve as market prices fall and with the introduction of biosimilars. |
| Augustine 2014[248] | Certolizumab for CD | The available data show that certolizumab pegol achieves similar therapeutic efficacy and health-related quality of life scores in CD patients as the other biological agents, but at a higher cost. |
| Thompson 2019[5] | Early biological treatment versus conventional treatment for CD | Whether early biologic therapy is more effective than conventional therapy for CD in adults is unclear due to a limited number of studies, insufficient data on endoscopic remission, and heterogeneity of existing studies. Available evidence does not suggest a clear and consistent benefit for early biologic therapy across outcomes. |
| Young 2019[249] | Biologics versus Immunomodulators or antibiotics for fistulising CD | The conclusions of the identified economic studies were not consistent regarding the comparative cost-effectiveness of biologics versus immunomodulators or antibiotics. Two primary studies concluded that biologics were cost-effective compared to various standard care treatments; however, one primary study suggested that infliximab was not cost-effective compared to treatment with mercaptopurine and metronidazole. |
| Smart 2014[250] | Infliximab for CD | Studies have been found to be very heterogeneous depending on setting, costs assumed and clinical data. Within the UK setting, infliximab has been found to be cost-effective with increased costs of around £25,000 per quality adjusted life year gained. |
| Chen 2020[251] | Infliximab for CD | Reimbursing infliximab for moderate-to-severe CD in Chinese patients was highly attractive, costing Chinese public insurance payers less than the 2018 Chinese gross domestic product per capita (GDPPC) to gain 1 QALY. |
| Vasudevan 2019[149] | Optimizing anti-TNFs | Optimizing anti-TNF therapy to achieve objective disease control seems to be cost-effective at conventional willingness-to-pay thresholds in a number of clinical settings. |

| | | |
|---|---|---|
| Yi-Sheng 2018[252] | Biologics dose escalation | There is a need for prospective randomized studies to assess the effectiveness of different dosing strategies. Once clinical effectiveness is established, economic evaluations are needed in order to determine the cost-effectiveness. |
| Schneider 2016[154] | Vedolizumab for IBD | Current literature suggests that from a cost-effectiveness perspective, vedolizumab might be a reasonable option for first- and second-line therapy for moderate to severe ulcerative colitis. To date, there are no studies to suggest that vedolizumab would be the most cost-effective option for first-line therapy for moderate to severe CD. However, studies suggest that vedolizumab has a role later on in an individual's treatment course. |
| **Therapeutic drug monitoring** | | |
| McNeill 2020[200] | TDM | TDM for thiopurines is likely to confer significant cost savings through improved clinical outcomes but remains underutilised due to limited RCT data. Reactive TDM of infliximab optimises dosing and reduces expenditure by over 50%, without affecting clinical outcomes. Proactive infliximab TDM may confer long-term clinical benefit but is only modestly cost-effective. Cost-effectiveness data for TDM of biologics other than infliximab are absent. TDM of methotrexate is not clinically useful or cost-effective. |
| Freeman 2016[253] | TDM | Testing is not cost-effective for infliximab. |
| Martelli 2017[194] | TDM | TDM strategy leads to major cost savings related to anti-TNF therapy in both IBD and rheumatoid arthritis patients, with no negative impact on efficacy. |
| Yao 2020[160] | TDM | TDM-guided strategies were consistently found to be cost-saving or cost-effective. |
| **Other** | | |
| Greveson 2013[254] | Mycobacterial infection detection using IGRA in subjects suitable for anti-TNF therapy | The use of a simple screening protocol for latent tuberculosis infection incorporating IGRA (T-SPOT.TB) in place of Mantoux Tuberculin skin test in a largely BCG vaccinated population, many using immunomodulatory agents, is a cost-effective strategy. |
| de Groof 2019[209] | Cost-effectiveness biologics vs early surgery RCT, ileocecal CD | Mean Crohn's disease total direct health care costs per patient at 1 year were lower in the resection group compared with the infliximab group (mean difference €-8931; 95% CI €-12 087 to €-5097), thus laparoscopic ileocecal resection is a cost-effective treatment option compared with infliximab. |
| Aksan 2021[155] | Ferric carboxymaltose | Ferric carboxymaltose was projected to be the most cost-effective intravenous iron therapy in Switzerland, increasing the number of responders and leading to cost savings for health care payers. |
| Tsertsvadze 2015[255] | Elemental nutrition for CD | Limited evidence indicates potential benefits of elemental nutrition against no intervention in the maintenance of remission and prevention of relapse in adult patients with CD. |

Abbreviations: IBD (inflammatory bowel disease); CD (Crohn's disease); therapeutic drug monitoring (TDM).

## TABLE 4. DISEASE MONITORING STRATEGIES AND COSTS

| Disease monitoring strategy | Patient centred | Cost | Inflammation centred | Prediction of disease course | Prediction of disease complications |
|---|---|---|---|---|---|
| Patient reported outcomes | +++ | low | - | + | - |
| Composite clinical outcomes | +++ | low | - | + | - |
| Serum biomarkers | ++ | low | + | + | + |
| Faecal biomarkers | ++ | low | ++ | ++ | ++ |
| Intestinal ultrasound | ++ | moderate | ++ | ++ | |
| Cross sectional imaging | + | high | +++ | ++ | +++ |
| Endoscopy | ++ | high | +++ | +++ | ++ |
| Histology | + | high | +++ | +++ | ++ |

# TABLE 5. MEASURES TO REDUCE DIRECT AND INDIRECT COSTS IN INFLAMMATORY BOWEL DISEASE (IBD)

| DIRECT COSTS | Measures | How to introduce these measures | How to analyse the effectiveness of these measures |
|---|---|---|---|
| **IBD nurse driven clinics** | Co-ordination of clinical inpatient and outpatient care | Introduction of nurse-led advice lines/virtual or face-to face clinics | Measure costs of health care visits and number of health care visits (emergency room visits, unscheduled outpatient visits, hospital admission, appointments with IBD physicians etc). before and after initiation of IBD-nurse driven clinics |
| | Telephone advice / helpline | Training nurses as specialised IBD clinical nurse consultants trained in care coordination, counselling prior to starting therapy and monitoring and follow-up of therapy, management of flare-ups, preventive care and psychosocial support | Uptake of preventative health initiatives |
| | Co-ordination of transitional care | Develop protocol or algorithms to guid use of IBD nurses | Patient satisfaction eg QUOTE-IBD survey |
| | Biologic therapy support | Ensure health care provider and insurers consider reimbursement | |
| | Improving tightness of care, coordination, and follow-up.<br>Telephone follow-up (s.c. therapy) | | |
| **Introducing e-Health technologies** | Telemedicine (IBD experts, IBD nurses), Virtual clinics, patient self-evaluation applications (web-based and linked to electronic medical records) | Decide on national or regional e-Health solutions | Measure costs of health care visits and number of health care visits (emergency room visits, unscheduled outpatient visits, hospital admission, appointment with IBD physicians etc). before and after initiation of e-Health |
| | Improving self-disease management | Establish multidisciplinary forums to discuss and co-ordinate patient care | Measure provider and patient satisfaction with eHealth model of care using patient-reported experience measures, decisional conflict scale (DCS), decision self-efficacy |

| | | | |
|---|---|---|---|
| | | | scale (DSES) medication adherence eg Medication Adherence Report Scale-5 (MARS-5) |
| | Reduce emergency room presentations and hospitalizations | Training of IBD patients and health care providers on e-Health system | |
| | Increase adherence to therapy | Introduce electronic medical record trouble shooting capabilities in jurisdiction | |
| | e-health tools to support consumer self-management and easier care navigation | Equip patients with IBD specific apps to facilitate self-management, shared decision making and increase medication adherence | |
| | Having published key performance indicators for IBD treatment centres (smoking, steroids, opiates, admissions, surgeries etc) | | |
| **Prioritization of drug use** | Fast-track drug approval | Engage with regulatory/administrative bodies to fast-track drug approvals | Measure patient disease activity, steroid exposure, Emergency room visits, Unscheduled outpatient visits, Hospital admissions |
| | Personalized medicine | Commissions in each country to review optimal drug prioritization and disseminate guidelines within each country or country bloc | Perform drug cost-effectiveness analyses |
| | Data collection and data mesh strategies to enable rapid data insights on comparative efficacy of existing drugs | Introduce step-up approaches to drug therapy | Review how often guidelines are followed in disease management |
| | Data collection and data mesh strategies to enable rapid rapid insights into actual value and positioning of new agents | Restrict access to high-cost therapies until only after low-cost drugs have been tried or only for specific high-risk phenotypes/presentations | |

| | | | |
|---|---|---|---|
| | | Use objective biomarkers to demonstrate treatment response to access ongoing treatment<br><br>Generate evidence-based approach on cost-effectiveness of drug prioritization and disseminate to policy maker and health care providers<br><br>Introduce incentives for data sharing | |
| **Sustainable health-financing mechanisms** | Reducing drug / consultation / hospitalization / surgery costs<br><br>Utilize predictors of high costs/high-cost patients in IBD:<br><br>*Uncontrolled disease (visits, hospitalization, drugs, escalation of therapy, surgery, disease-specific costs)*<br><br>*Steroid use (complications, infections)*<br><br>*Comorbidities (extraintestinal manifestations, psychiatric illnesses, infections i.e., C. difficile)* | Implement novel approaches to improving quality via education and training of clinicians, patients and policy makers<br><br>Implement national and international guidelines<br><br>Implement strategies to assess the appropriateness and efficiency of health care delivery<br><br>Ensure multispecialty, holistic care provision in clinics<br><br>Reduce delay in having patient see specialist to manage extraintestinal disease.<br><br>Provide access to mental health care | Measure health care visits and costs of care before and after the multispecialty and especially mental; health expertise is provided.<br><br>Measure variation of health care delivery from national and international guidelines<br><br>Assess of barriers to implementing guidelines<br><br>Evaluating novel models of care (such as values-based health care, integrated health care, participatory healthcare |
| **Value based health care** | Improving health care delivery models | Introduce IBD clinic models in all jurisdictions that include nurse specialists, social workers, dietitians, psychiatric health providers and other specialists | Assess value based on patient outcomes including patient-reported outcomes and the cost associated with achieving specific outcomes |

| | | | |
|---|---|---|---|
| | Improving effectiveness and value to IBD care | Collect patient outcome data including patient-reported outcomes and health care utilisation data | Assess improvements in quality of health care delivery based on feed-back loops and quality of care indicators |
| | Education | Implement clinical management software | |
| | Remove barriers to health care recourses utilization | Implement feed-back loops for continuous quality improvement | |
| | Continuity of care | Include patient reported outcomes in health services | |
| **De-escalation therapy / "exit" strategies** | Drug optimization | Implement Therapeutic Drug Monitoring | Determine how often de-escalation occurs and how often it can remain sustained in the de-escalated state |
| | Treat-to-target strategies | Use invasive and non-invasive marker of disease activity to determine de-escalation | Calculate costs savings for reducing drug costs and including costs for recurrences and re-initiation of drug |
| | Dissemination of guidelines | Implement national and international guidelines for initiating and de-escalating drug therapy | Measure patient disease activity, steroid exposure, Emergency room visits, Unscheduled outpatient visits, Hospital admissions |
| | Standardized protocols and algorithms for starting and stopping treatments | Generate guidance and algorithms to guide physicians on flow for de-escalation | Assess appropriateness of escalation/de-escalation of therapy |
| | Therapeutic drug monitoring (drug levels, antibodies) | Implement Virtual clinics to facilitate care-coordination and escalation and de-escalation of drug therapy | |
| | Shared decision-making supported by tools | Counsel patients on risk and benefit of de-escalation | |
| **Increase use of non-invasive biomarkers / monitoring** | CRP | Encourage use of non-invasive markers to guide therapeutic decision making | Measure patient disease activity, steroid exposure, Emergency room visits, Unscheduled outpatient visits, Hospital admissions |

| | | | |
|---|---|---|---|
| | Faecal calprotectin<br><br>Point-of-care intestinal ultrasound | Ensure these tests are available in all jurisdictions with IBD clinics<br><br>Ensure health care provider and insurers consider reimbursement of non-invasive tools<br><br>Attempt to reserve invasive disease assessment for more severe presentations or dysplasia surveillance | Determine how often these tests are used, how often drug escalation is undertaken in relation to these tests being ordered |
| **Improving the transparency of the financial data** | **Health care spending in IBD by source:**<br><br>*Government or public or social insurance (National Health system)*<br><br>*Private insurance (mixed or not mixed type)*<br><br>*Out-of-pocket-money (primary care, emergency visits, hospitalization, traveling)*<br><br>*Philanthropy* | Engage with funding bodies to formulate sustainable models of care that prioritise access to care and quality care delivery<br><br>Governments and insurers to liaison with IBD experts to ensure appropriate algorithms for drug tiering | Provide access to nationally funded IBD health care<br><br>Provide access to privately funded IBD health care<br><br>Measure quality of health care delivery based on nationally/internationally recognised quality indicators<br><br>Determine how often and how rapidly other drugs need to be chosen other than what government or insurer is offering |
| **Environmental Risk Factor Modification** | Reduced incidence of IBD | Educate on smoking, indiscriminate use of antibiotics in children who may be first- or second-degree relatives of persons with IBD, reducing intake of highly processed foods, promote breast feeding | Measure patient disease activity, steroid exposure, Emergency room visits, Unscheduled outpatient visits, Hospital admissions |

| | | | |
|---|---|---|---|
| | Improved course of IBD disease severity | Educate and counsel on measures to reduce stress and increase physical activity<br><br>Promote healthy balanced diets and minimise diets high in animal fats/refined sugars and highly processed foods<br><br>Provide rapid step-up or top-down approaches to medical therapy<br><br>Public actions to increase visibility of the problem | Tracke smoking, antibiotic and processed food intake and correlating with evolving disease incidence |
| **INDIRECT COSTS** | | | |
| **Enable options for planning of care needs/early retirement** | Boosting abilities and hobbies to help patients, family and society | Encourage patients to develop problem solving skills, pursue alternate vocational training, or hobbies.<br><br>Encourage patients to discuss and plan care needs, retirement and minimise impact on carer/societal burden | Measure quality of life and IBD-related disability before and after retirement |

| | | | |
|---|---|---|---|
| | | Encourage patients to take advantage of supportive services | |
| **Reducing loss of productivity** (presenteeism) | Work environment, support, flexibility | Engagement of employers to increase work-place flexibility such as working from home and modifying duties<br><br>Ensuring there are adequate laws governing workplace rules for persons with chronic disease including IBD | Assess rates of absenteeism, presenteeism, disability as well as work productivity (e.g. work productivity activity index, WPAI) |
| **Reducing sick leave** (absenteeism) | Option to work from home, changing topic of work, flexibility | Engage employers to increase work-place flexibility such as working from home and modifying duties<br><br>Maximizing care through specialized IBD clinics, early diagnosis and treatment escalation<br><br>Ensure there are adequate laws governing workplace rules for persons with chronic disease including IBD | Assessrates of absenteeism, presenteeism and disability |
| **Holistic healthcare and other** | Implementation of preventive medicine strategies (i.e vaccinations)<br><br>Patient education | Implement check-lists to increase uptake of preventive medication strategies<br><br>Joint action with IBD Patients Organizations | Uptake of preventive medicine strategies eg vaccinations/bone health<br><br>Patient Knowledge using tools eg CCKnow |

| | | | |
|---|---|---|---|
| | Collaboration with industry for new therapies/innovation | Development of patient education tools<br><br>Nurse-led disease management counselling and preventive medicine clinics<br><br>Investigator and sponsor led studies into novel therapies and models of care | Integration of evidence-based strategies into guidelines and public health policy |

# SUPPLEMENTARY FILE

## WHAT COHORT DATA ARE AVAILABLE ABOUT THE HEALTH CARE COSTS OF INFLAMMATORY BOWEL DISEASE?

What follows is a review of representative direct and indirect cost studies from high-income countries (as defined by the World Bank). Articles in English were accessed on PubMed and Google Scholar. Studies selected for inclusion needed to be carried out in high-income countries during the biological era (i.e., 1998 onwards, when infliximab was introduced in the US), be based on defined populations or national patient registries or administrative (claims) databases, report data for cost per patient (prevalent or incident) and include direct and/or indirect costs. In countries where only single-hospital or multiple-hospital studies were reported, studies were included only if they met all other criteria. The search criteria for identifying studies were: 'cost,' 'direct cost,' 'indirect cost,' 'inflammatory bowel disease,' 'Crohn's disease,' 'ulcerative colitis,' 'indeterminate colitis,' and 'inflammatory bowel disease unclassified.' Only full-length articles were reviewed; abstracts and conference reports were disregarded. Articles that reported total costs per disease, but not costs per patient, were excluded. Supplementary Table 1 summarizes, as best we can, the pertinent results of these studies.

## DIRECT HEALTH CARE COSTS OF INFLAMMATORY BOWEL DISEASE

### Europe

There have been several European, population-based cohort studies of the direct costs of IBD care. Burisch *et al*. (2015) reported on first-year cost data for 1,367 newly diagnosed patients (710 ulcerative colitis, 509 Crohn's disease, 148 IBDU), who were recruited beginning in 2010 from 20 European countries and Israel.[1] All costs were calculated using the Danish Health Cost Register. The mean annual direct health care cost for Crohn's disease patients was calculated as €5,942, for ulcerative colitis it was €2,753, and for IBDU it was €2,898. In Crohn's disease, standard treatment accounted for 15% of expenditure (5-ASA 5%), biologics for 20%, investigations for 31%, and surgery for 34%. In ulcerative colitis, standard treatment accounted for 30% of costs (5-ASA 27%), biologics for 8%, investigations for 45%, and surgery for 17%. The percentage of patients treated with biologics rose steadily during the years of follow-up, particularly in Crohn's disease. The percentage of Crohn's disease patients requiring surgery also increased during this period. Disease phenotype was found to be a cost-driver: younger patients were more expensive to treat, as were Crohn's disease patients classified as B2 and B3, as well as ulcerative colitis patients with more extensive disease. Costs for IBD patients were higher in Western European countries than in Eastern Europe, particularly for biological medications.

The same authors published a five-year follow-up study in 2020 in which the costs per individual country were used and the disease diagnoses were reclassified as needed.[2] The cohort comprised 1,289 IBD patients: 1,073 (83%) from Western Europe and 216 (17%) from Eastern Europe. The mean annual cost per IBD patient was €2,609 (median €446). For Crohn's disease, the mean annual cost was €3,542 (median €717), for ulcerative colitis it was €2,088 (median €408), and for IBDU it was €1,609 (median €415). Costs were highest in the first year after diagnosis, and then declined significantly during follow-up. Hospitalizations and investigations accounted for over 50% of costs during the first year, but in subsequent years there was a steady increase in expenditure on biologics, which accounted for 73% of costs in Crohn's disease, and 48% in ulcerative colitis, in the fifth year after diagnosis. The mean annual cost for biologics in all IBD patients was €866; for Crohn's disease it was €1,782, for ulcerative colitis it was €286, and for IBDU it was €521. However, most patients

were not treated with biologics and mean prices therefore low. Overall, biological therapy accounted for 33% of all costs, hospitalizations for 25%, investigations for 22%, surgery for 9%, and standard medications for 8%. In the first year after diagnosis, costs were driven by hospitalizations and investigations (amounting to more than 50% of total costs). In the fifth year, costs were driven by biological treatment (73% of the total costs in Crohn's disease, 48% in ulcerative colitis). The mean annual cost of biologics in Western Europe was twice that in Eastern Europe. Higher costs were associated with diagnosis of Crohn's disease, biological treatment, first year of diagnosis, current smoking in Crohn's disease, previous smoking in ulcerative colitis, disease severity B3 in Crohn's disease, and extent E2 and E3 in ulcerative colitis. (A description of the cost structures in the participating countries is given in Supplementary Table 1 of Burisch *et al*. 2020.)

Khalili *et al.* reported a cost analysis of data abstracted from the Swedish National Patient Register of prevalent IBD cases. In patients aged 18–64 years, the mean annual cost per Crohn's disease patient was $10,094, of which biologics accounted for $4,495 (45%), standard medications for $1,335 (13%), outpatient visits for $1,926 (19%), and hospitalizations for $2,338 (23%).[3] In ulcerative colitis, the total mean annual cost was $5,924; biologics accounted for 25% of this figure. Hospitalization charges were higher in older subjects; however, it was not stated whether these charges included treatment for comorbidities. In both the prevalent and incident cohorts, 15% of Crohn's disease patients and 9% of ulcerative colitis patients accounted for 50% of the annual total cost.

Lo *et al*. retrieved data from the Danish National Patient Registry for 213 Crohn's disease and 300 ulcerative colitis patients in Copenhagen between 2003–2016.[4] The mean annual direct cost per Crohn's disease patient for hospitalization was €6,600, surgery was €4,100, biologics was €700, standard medication was €736, and investigations were €290. For ulcerative colitis, the corresponding costs were €4,700, €2,900, €300, €120, and €535, respectively. Vadstrup *et al*. (2020) reported on a much larger Danish cohort, stratified by year of diagnosis, between 2003–2015.[5] Hospitalization was the chief cost-driver in the first year in both Crohn's disease and ulcerative colitis, and outpatient charges were the greatest driver in the fifth year. Medication costs remained low, possibly indicating a limited use of biologics.

Van der Valk *et al*. (2014) reported cost data in the Dutch physician-generated COIN study.[6] The total annual cost per patient was found to be lower in ulcerative colitis than Crohn's disease. Costs for biologics and hospitalizations accounted for 64% and 19%, respectively, of the total cost in Crohn's disease. By comparison, in ulcerative colitis biologics accounted for 19%, and hospitalizations for 14% of the total cost. In Crohn's disease, medication costs were driven by anti-TNF medications (64% of the total cost, with 23% of patients treated with anti-TNF). In ulcerative colitis, medication costs were driven by anti-TNF and 5-ASA (54% of the total cost, with 4% of patients treated with anti-TNF and 64% treated with 5-ASA). Predictors of high health care costs in Crohn's disease included current flare-ups and penetrating disease, and in ulcerative colitis the predictors were current flare-ups and current ileostomy.

Aldeguer and Sicras-Mainar (2016) in Spain reported on 285 adult ulcerative colitis patients for the period 2002–2012.[7] The mean direct annual cost per ulcerative colitis patient was €1,754, of which medications accounted for 28% (biologics were not mentioned). By contrast, Pillai *et al*. (2019) in Switzerland found the total annual cost for Crohn's disease to be €9,504 and for ulcerative colitis to be €5,704, with medications accounting for 70% and 68% of these costs, respectively.[8] Benedini *et al*. (2012) in Italy reported an annual total cost of direct care in Crohn's disease of €18,838, with medications accounting for 50% of this figure.[9]

**Australia**

Two studies were reported from Melbourne. Niewiadomski *et al*. (2015), in a prospective study between 2007 and 2013, reported a mean annual cost per Crohn's disease patient of $10,477 AUD,

and for ulcerative colitis of $6,292 AUD.[10] Predictors of high costs during the first year of Crohn's disease were perianal disease, L2–L3, and B2–B3; for ulcerative colitis, the predictors were disease extent E2–E3 and a CRP greater than ten. High-cost outliers with Crohn's disease (11% of patients) or ulcerative colitis (10%) accounted for 42% and 36%, respectively, of total costs. Jackson *et al*. (2017) performed a retrospective tertiary centre cost analysis for one year, ending March 2015.[11] The annual median total cost for Crohn's disease was $15,648 AUD, while for ulcerative colitis it was $5,017 AUD. Cost drivers were active disease and hospitalization. Outpatient services costs were higher for Crohn's disease than for ulcerative colitis.

**Asia**

In Asia, access to drugs and the types of approved and reimbursed drugs vary between countries. For instance, in Japan all prices are fixed by the government. Since the Ministry of Health, Labour and Welfare in Japan reimburses all the costs of IBD care, including high-cost drugs such as biologics, neither patients nor hospitals bear the costs of care.

Kim *et al*. (2019) analysed data from a South Korean patient claims database between 2005–2015, when the Crohn's disease patient population increased from 4,340 to 12,251, and ulcerative colitis from 10,701 to 23,811.[12] The mean annual direct health care cost of Crohn's disease increased in this period from $1,178 to $3,192. For ulcerative colitis the direct costs increased from $413 to $798. The annual rate of biologic usage escalated from 39·8% to 93·1% in Crohn's disease, and from 0·4% to 84·5% in ulcerative colitis. In 2015, anti-TNF therapies accounted for 69% of the total cost in Crohn's disease, and 49% in ulcerative colitis. Treatment with anti-TNF was the strongest predictor of high costs among both ulcerative colitis and Crohn's disease patients. Other predictors of higher costs were young age at onset, hospitalization, and surgery.

Lee *et al*. (2020) also showed that the cost of IBD in South Korea is driven by biological medications. In the period 2010–2012, the total direct cost in Crohn's disease was $3,658 in the first year, $2,109 in the second year, and $2,120 in the third year.[13] The costs of biologics for those same years were $774 (20% of the first-year total cost), $1,052 (50%), and $1,274 (60%), respectively. In ulcerative colitis, the corresponding total annual costs were $1,758, $1,185, and $1,117, respectively; biologics accounted for $108 (6%), $215 (18%), and $282 (25%) of these total costs, respectively.

A study in Hong Kong found that hospitalizations and 5-ASA usage accounted for 56% of the total direct costs in the first two years after a new IBD diagnosis.[14] Direct costs were higher in the first year. Surgery and low haemoglobin on presentation were associated with higher costs.

**North America**

*United States*

Using the PharMetrics commercial insurance claims database, Kappelman *et al*. (2008) determined the mean annual cost for prevalent patients with IBD for the years 2003 and 2004 in the US.[15] The mean annual patient cost for Crohn's disease was $8,265, and for ulcerative colitis it was $5,066. The most expensive item in the breakdown for Crohn's disease was medications ($2,919), while in ulcerative colitis it was outpatient services ($1,768). Younger age (under 20 years) was associated with higher costs in both diseases. In Crohn's disease, biologics accounted for 11% of the total cost, but in ulcerative colitis it was less than 2%. However, this study analysed data gathered prior to widespread use of biologics for the treatment of ulcerative colitis. In a secondary analysis, Kappelman *et al*. (2011) showed that patients with Crohn's disease had more medical and surgical hospitalizations than patients with ulcerative colitis.[16] They also found that females and younger patients had more hospitalizations.

In an analysis of eleven US health insurance plans, Park *et al*. (2015) extracted data from a large, administrative database of 5,090 patients with Crohn's disease.[17] For the entire cohort, the mean annual cost per patient was $18,637; for patients under the age of 18 it was $22,796, while for

patients older than 18 it was $18,095. High-cost (28% of patients accounting for 80% of costs) and low-cost (remaining 72%) patients had costs of $45,602 and $8,153, respectively; 20% of patients accounted for 80% of the mean annual cost. Biologics accounted for 30% of total yearly outlay, non-biologics 16%, and hospitalizations 23%. A subsequent report by Park *et al*. (2020) described costs for 23,720 Crohn's disease and 29,062 ulcerative colitis patients with either commercial insurance or Medicare Advantage coverage and listed in the Optum Research Database.[18] Extrapolating from data shown in graphical form, the mean annual cost per IBD patient was determined to be $22,000 in 2008 and $30,000 in 2016. For Crohn's disease, the mean annual cost in the first year was $30,000, rising to $38,000 by year 10; for ulcerative colitis, the corresponding costs were $25,000 and $15,000, respectively. Strong drivers of cost were being younger than 18 (where the cost was 1·4 times higher) and use of biologics (2·4 times higher). The rise in costs for Crohn's disease, compared with the decrease of costs for ulcerative colitis, was attributed to the more widespread use of biological medications among Crohn's disease patients.

Working with the Optum Research Health database, Cohen *et al*. (2015) showed that the direct health care costs in ulcerative colitis patients varied with the severity of the disease, with moderate-severe patients costing $22,874 per year versus $15,378 for a mixed total cohort.[19] Pilon *et al.* (2020) estimated the total cost per ulcerative colitis patient to be $18,198 per year.[20]

Dielemann *et al.* (2020) estimated annual health care spending in the US between 1996 and 2016 based on datasets that together covered 87% of all health-care spending during that period. After adjusting for changes in inflation, population size, and age groups, health care spending for IBD was estimated to have increased at an annualized rate of 5.9% and spending in 2016 was estimated to be $25.3 billion (95%CI 22.3-28.7). Generally, health conditions with the greatest changes in spending, such as rheumatoid arthritis and IBD, were also those that saw the introduction of specialty drug treatments, including biologics, during the period.[21]

*Canada*

Bernstein *et al*. (2012) used the University of Manitoba IBD Epidemiological Database to analyse cost by age, and found that the annual costs for Crohn's disease were highest in patients younger than 18 years, at $4,174 CAD, followed by age groups 19–64 years at $3,875, and 65 years and older at $589.[22] The corresponding costs for ulcerative colitis were $3,364, $2,715 and $920, respectively. Targownik *et al*. (2019), using the same database, showed that in the period 2005–2015 the mean direct cost per Crohn's disease patient increased from $4,640 to $10,747 CAD, and from $2,194 to $5,065 CAD for ulcerative colitis patients.[23] The main driver of these increases was the more widespread use and earlier adoption of anti-TNF therapy over time. While the mean annual cost for hospitalizations decreased for Crohn's disease patients, it increased for ulcerative colitis patients. Higher per capita costs were also associated with being younger than 25 years and being male. These and other Canadian studies of direct costs were reviewed by Kuenzig *et al*. (2019), who found substantial variation (two-fold or more) among the provinces of Manitoba, Alberta, and Quebec.[24] Treating newly diagnosed Crohn's disease or ulcerative colitis was 68% and 100% more expensive, respectively, than treating patients four years after a diagnosis. IBD patients receiving infliximab were always more expensive to treat than in the years prior to their receiving infliximab.[23] Biologics were used by 14·2% of Crohn's disease and 4 ·1% of ulcerative colitis patients and were significant drivers of medication costs in all provinces. Overall, the direct health care cost of IBD in Canada in 2018 was estimated to be $1·28 billion annually, or roughly $4,731 CAD per person with IBD.[24]

## INDIRECT HEALTH CARE COSTS OF INFLAMMATORY BOWEL DISEASE

### Europe

A study from Sweden by Khalili *et al*. (2020) used nationwide patient registries to analyse two cohorts: an incident cohort (2010–2013) and a prevalent cohort (2014), with a follow-up of one year.[3] The authors calculated costs resulting from lost productivity, including sick leave and disability pension. The mean cost per patient-year for total productivity losses was higher for Crohn's disease than for ulcerative colitis, both in the incident (Crohn's disease, $12,102; ulcerative colitis, $8,852) and prevalent cohorts (Crohn's disease, $12,717; ulcerative colitis, $8,209). Patients with incident Crohn's disease had higher mean costs for sick leave and lower costs for disability pension than prevalent patients (sick leave, $5,858 vs. $3,900; disability pension, $6,243 vs. $8,816). The respective incident versus prevalent costs for ulcerative colitispatients were sick leave, $4,073 vs. $3,118; disability pension, $4,778 vs. $5,091. In the prevalent cohort, the incremental increase in costs related to lost productivity compared to the respective general population was $6,771 for Crohn's disease and $2,491 for ulcerative colitis. Productivity losses in the prevalent cohort accounted for the majority of the total (direct and indirect) health-related indirect cost (56% for Crohn's disease, 59% for ulcerative colitis).

Two studies of population-based Danish cohorts have been reported. Lo *et al*. (2019) recruited incident patients with IBD diagnosed prospectively between 2003 and 2004 in the Copenhagen area, with follow-up continuing until 2013/2014.[4] The median annual total indirect cost per patient was €2,700 in Crohn's disease and €2,500 in ulcerative colitis. Data for the total indirect costs included paid sick leave (€1,100 in Crohn's disease and €1,100 in ulcerative colitis), social security benefits (€1,900 in Crohn's disease and €1,500 in ulcerative colitis), and loss of revenue from income tax (€700 in Crohn's disease and €800 in ulcerative colitis). During follow-up, it was determined that the total health care cost (direct plus indirect) was dominated by indirect costs. Interestingly, indirect costs were not significantly higher in IBD patients than in a non-IBD control population; this might reflect the fact that the extensive (compared to non-Scandinavian countries) Danish welfare system is able to support IBD patients and absorb both income and health care expenses.

A second Danish study by Vadstrup *et al*. (2020) was a national register-based study on incident Crohn's disease and ulcerative colitis patients diagnosed between 2003 and 2015 that analysed the societal costs incurred within five years of a diagnosis, including the indirect costs of lost productivity.[5] In both Crohn's disease and ulcerative colitis, the mean annual productivity losses per patient were highest in the first year after diagnosis and decreased in subsequent years (first year vs. fifth year: Crohn's disease €3,990 vs. €3,155; ulcerative colitis €2,499 vs. €1,535). Productivity losses in the first year after diagnosis accounted for 31% and 37% of total costs in Crohn's disease and ulcerative colitis, respectively and, together with hospital admissions, were the main cost drivers in the first year after diagnosis. In the subsequent four years, lost productivity (except for the second year in Crohn's disease) exceeded all other costs and was the main cost driver among both ulcerative colitis and Crohn's disease patients.

Two studies from the Netherlands have reported on indirect costs in IBD. The first study by van der Valk *et al*. (2014) was a multicentre study with voluntary patient participation.[6] The mean annual cost of lost productivity (including sick leave of patients and their caregivers) was €1,304 in patients with Crohn's disease and €1,156 in those with ulcerative colitis; this represented 16% and 36% of total costs in Crohn's disease and ulcerative colitis, respectively. The second study, by van Gennep *et al*. (2021), was cross-sectional and conducted in outpatient clinics at four hospitals in Amsterdam, again with voluntary patient participation, and it analysed the costs of overall work productivity losses (measured using the Work Productivity and Activity Impairment Questionnaire).[25] The mean annual cost per IBD patient for overall work productivity losses was €6,597, mostly attributable to presenteeism (€5,478), less so to absenteeism (€1,738). The highest overall costs for loss of work

productivity were in patients using second or third classes of biological treatment (€8,756 and €19,468, respectively), while the lowest costs were in patients naïve to biologics and immunomodulators (€4,756). Significantly higher costs for overall losses of work productivity were found in patients with active disease, reduced health-related quality of life, severe fatigue, and active perianal disease (Crohn's disease patients only).

In Spain, Aldeguer *et al*. (2016) published a retrospective, multicentre study using outpatient records from an administrative medical database of patients with ulcerative colitis diagnosed between 2002 and 2012.[7] The mean annual cost of lost productivity was €399, including €311 for sick leave and €88 for medical visits. Indirect costs represented 18·5% of the total costs. Factors impacting costs were age (negative effect), ulcerative colitis family history, diarrhoea, and psychological problems. The Swiss IBD Cohort Study (a national prospective cohort study recruiting patients from academic and non-academic centres across Switzerland), by Pillai *et al*. (2019), analysed the evolution of treatment and its related costs in the period 2006–2016.[8] The mean annual indirect cost per patient from lost productivity (absenteeism, as quantified using patient-reported data) was €1,339 in Crohn's disease and €707 in ulcerative colitis. Indirect costs represented 12·3% of the total (direct plus indirect) mean annual cost per patient in Crohn's disease, and 11·0% in ulcerative colitis. Annual indirect costs declined significantly by an average of 9% for Crohn's disease and 28% for ulcerative colitis during the study period; however, this decrease was less marked after controlling for patient and disease characteristics, especially for Crohn's disease.

In Italy, Benedini *et al*. (2012) conducted an observational, prospective, multicentre study of patients with Crohn's disease between 2006 and 2010 and reported the annual cost of lost productivity to be €2,784, while for non-health care costs (transport, home assistance) it was €899.[9] These indirect costs accounted for 24% of the total costs. Rankala *et al*. (2021) investigated costs incurred through presenteeism and absenteeism in randomly selected patients with IBD living in the Turku University Hospital district, Finland.[26] The costs of absenteeism (€741) and presenteeism (€644) in IBD were found to be similar. The same was true for Crohn's disease versus ulcerative colitis patients: absenteeism cost €724 in Crohn's disease patients and €750 in ulcerative colitis patients, while presenteeism cost €763 in Crohn's disease patients and €589 in ulcerative colitis patients.

In an Austrian study by Walter *et al*. (2020) of a very select patient population (members of the Austrian IBD Association), the mean annual indirect cost (absenteeism plus presenteeism) was determined to be €7,411.[27] Significantly higher costs were reported for patients with active disease (€12,377 vs. €6,040) and those being treated with biologics (€9,236 vs. €5,894).

In a study from Poland, Malinowski *et al*. (2015) assessed the indirect costs in 2012 of absenteeism among patients with several autoimmune diseases, including ulcerative colitis.[28] Data on absenteeism (including sick leave, short-term disability, and long-term disability – whether temporary or permanent) were obtained from the Information System of the Social Insurance Institution (which does not cover all employed people). Three common macroeconomic indicators were used for making estimates: gross domestic product (GDP), gross value added (GVA), and gross income (GI). The mean annual costs of absenteeism per ulcerative colitis patient were €1,260, €3,034, and €928 according to GDP per capita, GVA per worker, and GI per worker, respectively. The majority of these costs were attributable to sick leave, at €787, €1,896, and €580, respectively.

Finally, Mandel *et al.* (2014) assessed the indirect cost of IBD due to disability/sick leave and presenteeism in Hungary.[29] Using the human capital approach, the cost of disability and sick leave was €1,450 and €430 per patient per year, respectively, with a total productivity loss of €1,880. The corresponding costs of presenteeism were €2,605 and €2,410 for Crohn's disease and ulcerative colitis, respectively.

**Asia**

A single study from Japan by Yamabe *et al*. (2019) focused on the indirect costs of IBD.[30] This study was a retrospective, cross-sectional study that used pooled data of the annually fielded 2012–2014 Japan National Health and Wellness Survey. Respondents who self-reported IBD diagnoses were recruited via random sampling. Indirect costs were found to be 1·5-fold higher for patients with IBD than for controls (adjusted for baseline differences: 1,546,610 JPY vs. 1,067,331; $p$<0·001). Respondents with Crohn's disease reported numerically higher absenteeism, presenteeism, overall work impairment, and activity impairment than respondents with ulcerative colitis. However, indirect costs were similar in Crohn's disease and ulcerative colitis (1,645,068 JPY vs. 1,562,054, respectively; $p$=0·766).

**North America**

*United States*

There have been two reports using data from the Optum Health Care Solutions, Inc. employer claims database. These assessed indirect health care costs associated with ulcerative colitis in a privately insured, employed population in the US. A study by Cohen *et al*. (2015) for the years 2005 to 2013 evaluated the indirect use of resources, including lost productivity due to medically-related absenteeism and disability (both short- and long-term) during a one-year observation period.[19] The total adjusted indirect costs were, on average, twice as high for employees with ulcerative colitis than for non-ulcerative colitis controls (average annual cost: $4,125 vs. $1,961; $p$<0·001). Patients with moderate-to-severe ulcerative colitis had adjusted total indirect costs that were almost three times higher than those of controls ($5,666 vs. $1,960). A longer (1999 to 2017) follow-up study was published by Pilon *et al*. in 2020, with an observation period of around five years per patient[8]. In this study, patients with ulcerative colitis incurred $2,142 more in total indirect costs per patient-year than non-IBD controls (ulcerative colitis, $5,307 vs. controls, $3,165); the respective cost difference for absenteeism was $1,002 (ulcerative colitis, $2,592 vs. controls, $1,590), and for disability it was $1,140 (ulcerative colitis, $2,714 vs. controls, $1,575). Over half of the costs of absenteeism ($558) were driven by outpatient visits alone (ulcerative colitis, $1,729 vs. controls, $1,140). In an analysis of indirect costs during the first 12 months after diagnosis, patients with ulcerative colitis incurred $2,214 more in indirect costs than non-IBD controls ($4,784 vs. $2,570), including $1,478 more incurred through absenteeism ($2,993 vs. $1,515) and $736 more because of disability ($1,791 vs. $1,055).

A study by Park *et al*. (2020), using data from the Optum Research Database from the years 2007 to 2016, estimated lost wages due to medically-related health care visits in patients with IBD.[18] The total mean annual estimated cost of lost wages in individuals with IBD was ~$3,000, and patients with IBD incurred approximately three-fold-higher costs than their matched non-IBD controls (with an incremental indirect cost of ~$2,100). A novel study by Kahn *et al*. (2017) reported on productivity losses among 200 caregivers of paediatric Crohn's disease patients using a large-scale, US employer-based health insurance database.[31] The annual productivity losses of caregivers of paediatric Crohn's disease patients were 19·8% higher than those of controls (adjusted costs: $5,535 vs. $4,620). It was estimated that over the course of a Crohn's disease patient's childhood (age 13·4 to 18 years) the cumulative productivity loss incurred by the patient's caregiver cost $24,118, versus $18,957 for control caregivers.

*Canada*

The 2018 Impact of IBD in Canada report provided the estimated indirect health-related cost of IBD in Canada for the year 2018 to be C$4,781 per IBD patient.[32] The authors arrived at this figure after extrapolating from data about sick days and disability from North American and European studies. This estimate comprises lost earnings related to sick days and disability, premature retirement and premature death, and out-of-pocket expenses. The average lifetime cost of wages lost to premature retirement among IBD patients in the workforce was calculated to be C$1,044,498 per Crohn's disease patient and C$994,760 per ulcerative colitis patient. Elsewhere, data from Manitoba have

demonstrated increased levels of presenteeism and the correlation between levels of disability and presenteeism and health care utilization.[33–36] Costs were not attached to these findings but, considering that levels of disability and some of these health care utilizations (like hospitalizations) are similar in Manitoba to other countries worldwide, costs could be assigned in a country-specific way.

# SUPPLEMENTARY TABLE 1. DIRECT AND INDIRECT HEALTH CARE COSTS OF INFLAMMATORY BOWEL DISEASE

| Reference | Region, age, diagnosis, N | Duration | Direct cost estimates | | | | | Indirect cost estimates | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Study perspective | Disease perspective (N) | Cost per patient per year, mean | Cost per patient per year, median | Comments | Method of calculation of societal cost | IBD cohort compared with matched controls | Societal cost per patient per year, mean | Societal cost per patient per year, median | Comments |
| **Europe** | | | | | | | | | | | | |
| Burisch, 2015 | Europe, Israel. Age ≥15 y. | 2010 | Population-based inception cohort, 28 recruitment centres, Danish Health Costs Register (DRG). | West CD | € 6,232 | | 1. Predictors of higher costs: diagnosis, age, Montreal classification | | | | | |
| | West CD 405 | | | West UC | € 2,829 | | 2. Limited use of biologics: CD 20%, UC 8% | | | | | |
| | West UC 562 | | | West IBDU | € 2,944 | | | | | | | |
| | West IBDU 142 | | | East CD | € 4,812 | | | | | | | |
| | East CD 104 | | | East UC | € 2,464 | | | | | | | |
| | East UC 148 | | | East IBDU | € 1,814 | | | | | | | |
| | East IBDU 6 | | | West CD biologics | € 1,366 | | | | | | | |
| | | | | West UC biologics | € 273 | | | | | | | |
| | | | | West IBDU biologics | € 231 | | | | | | | |
| | | | | East CD biologics | € 399 | | | | | | | |
| | | | | East UC biologics | € 0 | | | | | | | |
| | | | | East IBDU biologics | € 0 | | | | | | | |
| Burisch, 2020 | Europe (20 countries) and Israel. | 2010-2015 | Population-based inception cohort, 28 recruitment centres, individual country costs, real-life setting. | West CD | € 3,972 | € 3,015 | 1. Follow-up of Burisch 2015, including re-classified patients | | | | | |
| | West CD 404 | | | West UC | € 2,414 | € 1,434 | 2. West-East differences | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | derive from disparate health systems and availability of biologics (Suppl. Table 1 in Burisch, 2020) | | | | | |
| | West UC 591 | | | West IBDU | € 7,183 | € 1,728 | 3. CD more expensive than UC or IBDU | | | | | |
| | West IBDU 78 | | | East CD | € 1,976 | € 522 | 4. Decreasing total cost, increasing cost of biologics, from year 1 onwards | | | | | |
| | East CD 84 | | | East UC | € 1,107 | € 409 | 5. Higher costs in severe phenotype, young age, smokers (CD and UC) | | | | | |
| | East UC 126 | | | East IBDU | € 866 | € 409 | | | | | | |
| | East IBDU 6 | | | | | | | | | | | |
| Khalili, 2019 | Sweden. Prevalence date 31-12-2014. | 2010-2015 | Swedish National Patient Register. US$ 2015 prices. | **Prevalent cases:** | | | 1. Anti-TNF: CD 64%, UC 36% | Human capital approach. Total population. Register-matched controls. | | | | 1. Lost productivity accounted for 56% and 58% of the total annual societal costs of CD and UC patients, respectively. |
| | CD | | | **CD, 18-64 y:** | | | 2. Greater expenditure on biologics in CD and in ages 18-64 y. | Productivity losses | Prevalent CD | US$ 12,717 | | 2. Prevalent CD patients had a mean avg. of 63 days of sick leave per annum, while UC patients had 41 days**.** |
| | ≥18 y 10,117 | | | Biologics | US$ 4,495 | | 3. Hospital charges higher in older individuals. | | Prevalent UC | US$ 8,209 | | 3. Incident CD patients of working age had a mean avg. of 29 days of sick leave per annum, while UC patients had 24 days. |
| | 18-64 y 7,663 | | | Other meds | US$ 1,335 | | | | Incident CD | US$ 12,102 | | |
| | >65 y 2,454 | | | Outpatient | US$ 1,926 | | | | Incident UC | US$ 8,852 | | |
| | UC | | | Hospitalization | US$ 2,338 | | | Sick leave | Prevalent CD | US$ 3,900 | | |
| | ≥18 y 19,762 | | | **CD, ≥ 65 y:** | | | | | Prevalent UC | US$ 3,118 | | |
| | 18-64 y 14,631 | | | Biologics | US$ 1,407 | | | | Incident CD | US$ 5,858 | | |
| | >65 y 5,131 | | | Other meds | US$ 1,881 | | | | Incident UC | US$ 4,073 | | |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Outpatient | US$ 2,092 | | | Disability pension | Prevalent CD | US$ 8,816 | | |
| | | | | Hospitalization | US$ 4,346 | | | | Prevalent UC | US$ 5,091 | | |
| | Incident cases, 2010-13: | | | **UC, 18-64 y:** | | | | | Incident CD | US$ 6,243 | | |
| | CD 4,028 | | | Biologics | US$ 1,471 | | | | Incident UC | US$ 4,778 | | |
| | UC 8,659 | | | Other meds | US$ 1,387 | | | | Prevalent UC | US$ 8,209 | | |
| | | | | Outpatient | US$ 1,447 | | | | | | | |
| | | | | Hospitalization | US$ 1,619 | | | | | | | |
| | | | | **UC, ≥65 y:** | | | | | | | | |
| | | | | Biologics | US$ 436 | | | | | | | |
| | | | | Other meds | US$ 1,925 | | | | | | | |
| | | | | Outpatient | US$ 1,706 | | | | | | | |
| | | | | Hospitalization | US$ 4,004 | | | | | | | |
| | | | | **Incident cases:** | | | | | | | | |
| | | | | **CD, age 18-64 y:** | | | | | | | | |
| | | | | Biologics | US$ 2,301 | | | | | | | |
| | | | | Hospital | US$ 5,152 | | | | | | | |
| | | | | **CD, age > 65 y:** | | | | | | | | |
| | | | | Biologics | US$ 759 | | | | | | | |
| | | | | Hospitalization | US$ 10,367 | | | | | | | |
| | | | | **UC, age 18-64 y:** | | | | | | | | |
| | | | | Biologics | US$ 831 | | | | | | | |
| | | | | Hospitalization | US$ 3,204 | | | | | | | |
| | | | | **UC, age > 65 y:** | | | | | | | | |
| | | | | Biologics | US$ 226 | | | | | | | |
| | | | | Hospitalization | US$ 7,556 | | | | | | | |
| Lo, 2019 | Copenhagen, Denmark. All ages. Incident cases. | 2003-2015 | National Patient Registry, Prescription Registry, Register of Causes of Death. | **CD:** | | | 1. CD had higher costs than UC. | Method not specified. Controls matched by age, sex, place of residence. | | | | 1. Indirect costs in IBD patients and controls were similar. |
| | CD 213 | | | Total | € 6,600 | € 4,900 | 2. In CD, cost of biologics increased upon follow-up. | Sick leave | CD | | € 1,100 | 2. Indirect costs in UC were driven by young age (17-40 y) and smoking. CD had no specific predictors. |
| | UC 300 | | | Hospitalization | € 4,100 | € 3,100 | 3. In UC, disease extent predicted cost. | | UC | | € 1,100 | 3. After the first year, the total costs were dominated by direct costs in CD patients, and by indirect costs in UC patients. |

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| | | | | Surgery | € 700 | € 0 | 4. In CD, phenotype did not predict cost. | Social security benefits | CD | | € 1,900 | |
| | | | | Biologics | € 736 | € 0 | | | UC | | € 1,500 | |
| | | | | Other meds | € 290 | € 117 | | Loss of revenue from income tax | CD | | € 700 | |
| | | | | Investigations | € 800 | € 600 | | | UC | | € 800 | |
| | | | | **UC:** | | | | | | | | |
| | | | | Total | € 4,700 | € 3,400 | | | | | | |
| | | | | Hospitalization | € 2,900 | € 2,000 | | | | | | |
| | | | | Surgery | € 300 | € 0 | | | | | | |
| | | | | Biologics | € 120 | € 0 | | | | | | |
| | | | | Other meds | € 535 | € 398 | | | | | | |
| | | | | Investigations | € 800 | € 600 | | | | | | |
| Vadstrup, 2020 | Denmark. | 2003-2015 | National register of patients. Five-year follow-up from diagnosis. € at 2016 value. | **Year 1:** | | | 1. CD more expensive than UC for direct costs. | Human capital approach. Matched controls (age, gender). | Year 1: | | | 1. Productivity for age group 18-65 y. |
| | CD 9,019 | | | **CD:** | | | 2. Year 1 costs were higher than subsequent years. | | CD | | | 2. Direct and indirect costs decreased each year after onset. |
| | UC 20,913 | | | Outpatients | € 3,851 | | | | Productivity | € 3,990 | | 3. CD more expensive than UC for indirect costs. |
| | | | | Hospitalization | €,4,745 | | | | Home care | € 33 | | 4. About one-third of year 1 total cost due to indirect costs. |
| | | | | Medications | € 399 | | | | UC | | | 5. In years 2-5, productivity losses were the main cost driver in CD and UC. |
| | | | | **UC:** | | | | | Productivity | € 2,499 | | |
| | | | | Outpatients | € 1,722 | | | | Home care | € 67 | | |
| | | | | Hospitalization | € 2,066 | | | | Year 5: | | | |
| | | | | Medications | € 476 | | | | CD | | | |
| | | | | **Year 5:** | | | | | Productivity | € 3,155 | | |
| | | | | **CD:** | | | | | Home care | € 24 | | |
| | | | | Outpatients | € 2,185 | | | | UC | | | |
| | | | | Hospitalization | € 107 | | | | Productivity | € 1,535 | | |
| | | | | Medications | € 187 | | | | Home care | € 39 | | |
| | | | | **UC:** | | | | | | | | |
| | | | | Outpatients | € 578 | | | | | | | |
| | | | | Hospitalization | € -3 | | | | | | | |

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| | | | | Medications | € 308 | | | | | | | |
| Van der Valk, 2014 | Netherlands. Patients ≥18 y. Prevalent cases followed at university and general hospitals. | 2011 data collected for three months. Data recalculated to 1 year. | COIN study: physician-instigated cohort from seven hospitals. 2011 prices. | **CD:** | | | 1. Biologics accounted for 64% of the cost in CD, 19% in UC. . | Method not specified | | | | 1.Total productivity losses were 16% and 39% of total costs in CD and UC, respectively. |
| | CD 1315 | | | Total | € 6,500 | | 2. Mesalamine and biologics were the main cost drivers among medications in UC; in CD, the main driver was biologics | Total productivity losses | CD | € 1,304 | | |
| | UC 937 | | | Outpatients | € 456 | | | | UC | € 1,580 | | |
| | | | | Diagnostics | € 162 | | | Sick leave, patients | CD | € 1,156 | | |
| | | | | Medications | € 414 | | | | UC | € 1,448 | | |
| | | | | Biologics | € 4,157 | | | Sick leave, caregivers | CD | € 72 | | |
| | | | | Hospitalization | € 1,261 | | | | UC | € 60 | | |
| | | | | Surgery | € 40 | | | Lost earnings | CD | € 76 | | |
| | | | | **UC**: | | | | | UC | € 72 | | |
| | | | | Total | € 3,961 | | | | | | | |
| | | | | Outpatients | € 274 | | | | | | | |
| | | | | Diagnostics | € 119 | | | | | | | |
| | | | | Medications | € 652 | | | | | | | |
| | | | | Biologics | € 748 | | | | | | | |
| | | | | Hospitalization | € 555 | | | | | | | |
| | | | | Surgery | € 33 | | | | | | | |
| Van Gennep, 2021 | Netherlands. Ages 16-63 y. | 2017-2019 | Amsterdam academic and non-academic hospitals. Questionnaire survey. Patients in active employment. | | | | | Human capital approach | IBD: | | | 1. Health-related quality of life correlated with productivity losses. |
| | CD 268 | | | | | | | | Absenteeism | € 1,738 | | 2. Active disease, perianal disease, and fatigue predicted productivity losses. |
| | UC 242 | | | | | | | | Presenteeism | € 5,478 | | 3. 50% of patients incurred productivity losses. |

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| | | | | | | | | | Overall work productivity losses | € 6,597 | | |
| Aldeguer, 2016 | Spain.<br>≥ 18 y<br>Prevalent cases,<br>≥ 1 y post-diagnosis. | 2002-2012 | Retrospective, outpatient records, administrative medical database. | **UC:** | | | 1. Most consultations were with a GP. | Estimations based on average national interprofessional wage. | | | | 1. Indirect costs were 18.5% of total costs. |
| | UC 285 | | | Total | € 1,754 | | 2. Medications: steroids + 5-ASA = 74%, IMM = 21%. Biologics not recorded. | Productivity losses | UC | € 399 | | 2. Drivers of indirect costs were age, UC family history, psychological comorbidities. |
| | | | | GP consult | € 251 | | | Sick leave payments | UC | € 311 | | 3. Indirect costs decreased with age. |
| | | | | GI consult | € 117 | | | Absenteeism (time spent at medical visits) | UC | € 88 | | |
| | | | | Hospitalization | € 853 | | | | | | | |
| | | | | Medication | € 497 | | | | | | | |
| | | | | Other | € 37 | | | | | | | |
| Pillai, 2019 | Switzerland.<br>Prevalent cases. | 2006-2016 | National prospective cohort study, continuous enrolment. Swiss DRG price codes. | **CD:** | | | 1. Intense drug use at enrolment: CD biologics, UC immunomodulators; at follow-up, CD and UC biologics and immunomodulators. | Human capital approach. Productivity losses (work absenteeism) based on subjects' recall. | CD | € 1,339 | € 686 | 1. Indirect costs were 12% and 11% of total costs in CD and UC, respectively. |
| | CD 1353 | | | Total | € 9504 | € 8230 | 2. Mean annual growth rate of total cost: CD 7%, UC 10%. | | UC | € 707 | € 170 | 2. Large measure of uncertainty of data recall. |
| | UC 1012 | | | Drugs | € 6618 | € 6678 | | | | | | |
| | | | | Inpatient | € 2188 | € 499 | | | | | | |
| | | | | Outpatient | € 698 | € 517 | | | | | | |
| | | | | **UC:** | | | | | | | | |
| | | | | Total | € 5704 | € 4578 | | | | | | |
| | | | | Drugs | € 3895 | € 3670 | | | | | | |
| | | | | Inpatient | € 1242 | € 241 | | | | | | |
| | | | | Outpatient | € 567 | € 383 | | | | | | |
| Benedini, 2012 | Italy.<br>Age 18-70 y. | 2006-2010 | Observational prospective study based on | **CD:** | | | | Human capital approach. Caregivers' expenses included. | CD: | | | |

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| | | | consecutive CD patient recruitment at participating hospitals. Data abstracted from four visits over one year. € 2011 prices. | | | | | | | | | |
| | CD 162. | | | Total | € 18,838 | | | | Productivity losses | € 2,784 | | |
| | | | | Medications | € 9,366 | | | | Transport, home assistance | € 899 | | |
| | | | | Hospitalization | € 1,688 | | | | Total indirect | € 3,685 | | |
| Rankala, 2012 | Finland | 2015-2016 | Random patient selection. Hospital records. National registers | | | | | Human capital approach | | | | Costs of absenteeism and presenteeism were largely similar. |
| | CD 102 | | | | | | | Absenteeism | CD | € 724 | | |
| | UC 218 | | | | | | | | UC | € 750 | | |
| | | | | | | | | | Men | € 531 | | |
| | | | | | | | | | Women | € 955 | | |
| | | | | | | | | | Biologics | € 933 | | |
| | | | | | | | | | Non-biologics | € 702 | | |
| | | | | | | | | Presenteeism | CD | € 763 | | |
| | | | | | | | | | UC | € 589 | | |
| | | | | | | | | | Men | € 495 | | |
| | | | | | | | | | Women | € 802 | | |
| | | | | | | | | | Biologics | € 1,079 | | |
| | | | | | | | | | Non-biologics | € 564 | | |
| Walter, 2020 | Austria | 2018-2019 | Members of Austrian CD/UC Association. Questionnaire. Median age 40 y. Median disease duration 9 y. Female: 74%. Employed: 64%. | | | | | Human capital approach. Recall in last seven days. Data calculated to mean one-year values. | IBD productivity losses | | | Limitations: very select cohort; recall limited to past week. |
| | CD 245 | | | | | | | | All patients | € 7,411 | | |
| | UC 165 | | | | | | | | Active disease | € 12,377 | | |
| | | | | | | | | | Remission | € 6,040 | | |

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| Malinowski, 2015 | Poland | 2012 | Social Insurance Institution | | | | | Macroeconomic indicators: | UC Absenteeism | | | Most costs caused by sick leave. |
| | | | | | | | | Gross Domestic Product (GDP) | GPD | € 1,260 | | |
| | | | | | | | | Gross Value Added (GVA) | GVA | € 3,034 | | |
| | | | | | | | | Gross Income (GI) | GI | € 928 | | |
| Mandel, 2014 | Hungary | 2012-2013 | Consecutive patients from 2 specialized centres providing biologic therapy | | | | | Human capital approach (HCA) & friction cost method (FCM). The 2010 national full disability pension rates used for comparison. | | | | Full disability pension (DP) more prevalent in CD (9.2%, p=0.009) but not in UC (6.6%, p=0.56) vs. background population (5.5%). |
| | CD 260 | | | | | | | Disability pension – HCA | IBD | € 1,450 | | Risk factors for DP in CD: age, previous surgery and arthritis/arthralgia. |
| | UC 183 | | | | | | | | CD | € 1,545 | | |
| | | | | | | | | | UC | € 1,310 | | |
| | | | | | | | | Disability pension – FCM | IBD | € 11.3 | | |
| | | | | | | | | | | | | |
| | | | | | | | | | Sick leave: | | | |
| | | | | | | | | | IBD | € 430 | | |
| | | | | | | | | | CD | € 395 | | |
| | | | | | | | | | UC | € 485 | | |
| | | | | | | | | Total productivity loss – HCA | IBD | € 1,880 | | |
| | | | | | | | | | CD | € 1,940 | | |
| | | | | | | | | | UC | € 1,795 | | |
| | | | | | | | | Total productivity loss – FCM | IBD | € 445 | | |
| | | | | | | | | Presenteeism | CD | € 2,605 | | |
| | | | | | | | | | UC | € 2,410 | | |
| **Australasia** | | | | | | | | | | | | |
| Niewiadomski, 2015 | Australia: Victoria, Melbourne. Incident cases. | 2007–2013 | Physician-initiated, population-based, prospective study. | **CD:** | | | 1. Biologics were 16% of CD cost, 1% of UC cost. | | | | | |
| | CD 146 | | | Total | AU$ 10,477 | AU$ 5,905 | 2. Cost drivers in CD: biologics, smoking, | | | | | |

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| | | | | | | | location, behaviour, perianal disease; in UC: disease location. | | | | | |
| | UC 96 | | | Medical hospitalization | AU$ 6,493 | AU$ 5,945 | | | | | | |
| | AUS$ | | | Surgical hospitalization | AU$ 15,283 | AU$ 10,444 | | | | | | |
| | | | | Medications | AU$ 3,366 | AU$ 2,165 | | | | | | |
| | | | | Diagnostic tests | AU$ 2,196 | AU$ 1,698 | | | | | | |
| | | | | **UC:** | | | | | | | | |
| | | | | Total | AU$ 6,292 | AU$ 4,752 | | | | | | |
| | | | | Medical hospitalization | AU$ 6,282 | AU$ 4,756 | | | | | | |
| | | | | Surgical hospitalization | AU$ 35,506 | AU$ 35,506 | | | | | | |
| | | | | Medications | AU$ 2,447 | AU$ 2,246 | | | | | | |
| | | | | Diagnostic tests | AU$ 1,825 | AU$ 1,374 | | | | | | |
| Jackson, 2017 | Australia: Melbourne. > 17 y. Prevalent cases. | April 2014 to March 2015 | Single tertiary hospital, retrospective. | **CD:** | | | 1. Cost data reported only as medians. | | | | | |
| | CD 93 | | | Total | | AUS$ 15,648 | 2. Hospitalization was 63% of total IBD cost, medications were 35%. | | | | | |
| | UC 87 | | | Remission | | AUS$ 4,613 | | | | | | |
| | AUS$ | | | Active | | AUS$ 5,495 | | | | | | |
| | | | | Hospitalized | | AUS$ 32,554 | | | | | | |
| | | | | Ambulatory | | AUS$ 9,602 | | | | | | |
| | | | | **UC:** | | | | | | | | |
| | | | | Total | | AUS$ 5,017 | | | | | | |
| | | | | Remission | | AUS$ 1,833 | | | | | | |
| | | | | Active | | AUS$ 1,776 | | | | | | |
| | | | | Hospitalized | | AUS$ 13,334 | | | | | | |
| | | | | Ambulatory | | AUS$ 4,966 | | | | | | |
| **Asia** | | | | | | | | | | | | |

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| Kim, 2019 | South Korea | 2005-2015 | Korean Health Insurance claims database, population based. Data calculated per annum. | **CD:** | | | 1. Predictors of cost: age at onset, hospitalization, surgery, anti-TNF. | | | | | |
| | CD 4,340 (in 2005) – 12,251 (2015). | | | 2006 | US$ 1,178 | | 2. Increase in annual use of biologics, 2006 – 2015: | | | | | |
| | UC 10,701 (2005) – 23,811 (2015). | | | 2007 | US$ 1,497 | | CD 39.8 – 93.1% | | | | | |
| | | | | 2008 | US$ 1,579 | | UC 0.4 – 84.5% | | | | | |
| | | | | 2009 | US$ 1,859 | | | | | | | |
| | | | | 2010 | US$ 2,138 | | | | | | | |
| | | | | 2011 | US$ 2,307 | | | | | | | |
| | | | | 2012 | US$ 2,521 | | | | | | | |
| | | | | 2013 | US$ 2,519 | | | | | | | |
| | | | | 2014 | US$ 2,853 | | | | | | | |
| | | | | 2015 | US$ 3,192 | | | | | | | |
| | | | | **UC:** | | | | | | | | |
| | | | | 2006 | US$ 413 | | | | | | | |
| | | | | 2007 | US$ 402 | | | | | | | |
| | | | | 2008 | US$ 400 | | | | | | | |
| | | | | 2009 | US$ 400 | | | | | | | |
| | | | | 2010 | US$ 423 | | | | | | | |
| | | | | 2011 | US$ 517 | | | | | | | |
| | | | | 2012 | US$ 574 | | | | | | | |
| | | | | 2013 | US$ 601 | | | | | | | |
| | | | | 2014 | US$ 679 | | | | | | | |
| | | | | 2015 | US$ 798 | | | | | | | |
| Lee, 2020 | South Korea. Incident cases. Costs converted from SK won to US$ at rate on 1st Nov 2017. | 2010-2012 | Korean Health Insurance claims database, nation-wide, population based. Comparison of cost before and after IBD diagnosis. | **CD:** | | | 1. Korea is an example of a country where UC cases still exceed CD. | | | | | |
| | CD 11,014 | | | Total | | | 2. Biologics are a cost-driver | | | | | |
| | UC 23,153 | | | Year 1 | US$ 3,658 | | 3. Total cost peaked in the first year after | | | | | |

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| | | | | | | | diagnosis, then decreased | | | | | |
| | | | | Year 2 | US$ 2,109 | | 4. First year costs driven by diagnostic procedures | | | | | |
| | | | | Year 3 | US$ 2,120 | | 5. Cost of biologics increased annually following diagnosis | | | | | |
| | | | | **UC:** | | | | | | | | |
| | | | | Total | US$ 1,758 | | | | | | | |
| | | | | Year 1 | US$ 1,185 | | | | | | | |
| | | | | Year 2 | US$ 1,117 | | | | | | | |
| | | | | Year 3 | | | | | | | | |
| | | | | **CD:** | | | | | | | | |
| | | | | Biologics | US$ 774 | | | | | | | |
| | | | | Year 1 | US$ 1,052 | | | | | | | |
| | | | | Year 2 | US$ 1,274 | | | | | | | |
| | | | | Year 3 | | | | | | | | |
| | | | | **UC:** | | | | | | | | |
| | | | | Biologics | | | | | | | | |
| | | | | Year 1 | US$ 108 | | | | | | | |
| | | | | Year 2 | US$ 215 | | | | | | | |
| | | | | Year 3 | US$ 282 | | | | | | | |
| Yamabe, 2019 | Japan. IBD. JPY. | 2012-2014 | Japan national Health and Wellness Survey | | | | | IBD self-reported diagnoses. Random patient sampling. | Indirect cost: | | | No difference between CD and UC patients |
| | | | | | | | | | IBD | JPY 1,546,610 | | |
| | | | | | | | | | CD | JPY 1,645,068 | | |
| | | | | | | | | | UC | JPY 1,562,054 | | |
| | | | | | | | | | Controls | JPY 1,067,331 | | |
| **Americas** | | | | | | | | | | | | |
| Bernstein, 2012 | Canada, Manitoba. All ages. Prevalent and incident cases. C$. | 2005-2006 | Manitoba Health Insurance Databases. See article for description of excluded cost items. | **IBD:** | | | 1. Chief cost drivers: year 1 of disease, hospitalization, surgery, infliximab | | | | | |
| | CD 3,735 | | | Prevalent | C$ 3,896 | | 2. Medication accounted for > 40% of overall costs | | | | | |
| | UC 3,640 | | | Year 1 of illness | C$ 6,611 | | 3. Costs were right-skewed: most costly 2% of IBD cases accounted for | | | | | |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | 23% of overall expenditure | | | | | |
| | | | | Hospitalization | C$ 13,495 | | 4. Age 19-64 y, values via extrapolation | | | | | |
| | | | | Surgery | C$ 18,749 | | | | | | | |
| | | | | Infliximab | C$ 31,440 | | | | | | | |
| | | | | **CD**: | | | | | | | | |
| | | | | Prevalent | C$ 4,232 | C$ 1,538 | | | | | | |
| | | | | Incident | C$ 6,750 | C$ 6,650 | | | | | | |
| | | | | Male | C$ 3,989 | | | | | | | |
| | | | | Female | C$ 4,407 | | | | | | | |
| | | | | Hospitalization | C$ 12,900 | | | | | | | |
| | | | | Surgery | C$ 18,154 | | | | | | | |
| | | | | Age ≤ 18 y | C$ 4,174 | | | | | | | |
| | | | | Age 19-64 y | C$ 3,875 | | | | | | | |
| | | | | Age 65-79 y | C$ 5,442 | | | | | | | |
| | | | | Age 80-102 | C$ 8372 | | | | | | | |
| | | | | **UC:** | | | | | | | | |
| | | | | Prevalent | C$ 3,552 | C$ 1,574 | | | | | | |
| | | | | Incident | C$ 3,190 | C$ 2,858 | | | | | | |
| | | | | Male | C$ 3,513 | | | | | | | |
| | | | | Female | C$ 3,588 | | | | | | | |
| | | | | Hospitalization | C$ 14,183 | | | | | | | |
| | | | | Surgery | C$ 19,763 | | | | | | | |
| | | | | Age ≤ 18 y | C$ 3,364 | | | | | | | |
| | | | | Age 19-64 y | C$ 2,714 | | | | | | | |
| | | | | Age 65-79 y | C$ 5,204 | | | | | | | |
| | | | | Age 80-102 | C$ 8,675 | | | | | | | |
| Coward, 2015 | Canada: Calgary, Alberta. Age ≥ 18y. C$. 2013 value. | 2001-2009 | Discharge Abstract Data-base claims, Hospitalization direct costs | **UC in-hospital:** | | | 1. Predictors of cost: calendar year, age, current smoker, disease extent, infliximab, length of admission. | | | | | |
| | | | | Medical | | C$ 5,499 | | | | | | |
| | UC 742 | | | Elective colectomy | | C$ 14,316 | | | | | | |
| | | | | Emergent colectomy | | C$ 23,698 | | | | | | |
| Targownik, 2019 | Canada, Manitoba. Prevalent cases. C$ | 2005-2015 | University of Manitoba IBD Database | **CD:** | | | 1. Anti-TNF escalated total cost | | | | | |
| | | | | Total | | | 2.Decreased hospitalization costs in UC failed to reduce overall cost | | | | | |
| | | | | 2005 | C$ 4,640 | | | | | | | |
| | | | | 2015 | C$ 10,747 | | | | | | | |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Anti-TNF | | | | | | | | |
| | | | | 2005 | C$ 671 | | | | | | | |
| | | | | 2015 | C$ 7,754 | | | | | | | |
| | | | | Hospitalization | | | | | | | | |
| | | | | 2005 | C$ 2,565 | | | | | | | |
| | | | | 2015 | C$ 1,426 | | | | | | | |
| | | | | **UC:** | | | | | | | | |
| | | | | Total | | | | | | | | |
| | | | | 2005 | C$ 2,194 | | | | | | | |
| | | | | 2015 | C$ 5,065 | | | | | | | |
| | | | | Anti-TNF | | | | | | | | |
| | | | | 2005 | C$ 38 | | | | | | | |
| | | | | 2015 | C$ 2,650 | | | | | | | |
| | | | | Hospitalization | | | | | | | | |
| | | | | 2005 | C$ 790 | | | | | | | |
| | | | | 2015 | C$ 1,016 | | | | | | | |
| Kappelman, 2008; Kappelman, 2011 | USA, 33 states: Northeast, Midwest, West, South. All ages. Prevalent cases. | 2003-2004 | Administrative database claims | **CD:** | | | 1. Predictors of higher cost in both sexes: age < 20 y | | | | | |
| | CD 9,056 | | | Total | US$ 8,265 | | 2. Predictors of greater need for hospitalization: diagnosis, age, gender, region, health insurance status | | | | | |
| | UC 10,364 | | | Surgery | US$ 1,026 | | | | | | | |
| | | | | Medical | US$ 1,567 | | | | | | | |
| | | | | ER | US$ 97 | | | | | | | |
| | | | | Endoscopy | US$ 266 | | | | | | | |
| | | | | Radiology | US$ 272 | | | | | | | |
| | | | | Outpatient | US$ 2,753 | | | | | | | |
| | | | | Medication | US$ 2,919 | | | | | | | |
| | | | | **UC:** | | | | | | | | |
| | | | | Total | US$ 5,066 | | | | | | | |
| | | | | Surgery | US$ 807 | | | | | | | |
| | | | | Medical | US$ 1,099 | | | | | | | |
| | | | | ER | US$ 44 | | | | | | | |
| | | | | Endoscopy | US$ 306 | | | | | | | |
| | | | | Radiology | US$ 165 | | | | | | | |
| | | | | Outpatient | US$ 1,768 | | | | | | | |
| | | | | Medication | US$ 1,393 | | | | | | | |
| Park, 2015 | USA, northeast, southeast, mid-west. | 2011-2013 | Accordant Health Services Administrative Database claims. | All patients | $ 18,637 | | 1. 28% of CD patients accounted for 80% of costs (drivers: anti-TNF, hospitalization) | | | | | |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Retrospective.<br>Age on 30th June 2021.<br>Costs include co-morbidities.<br>Patient co-payments excluded. | | | | | | | | | |
| | CD 5,090 | | | High-cost patients | $ 45,602 | $ 33,394 | 2. Anti-TNF accounted for 30%, and other medications for 16% of total cost | | | | | |
| | Men 2,197 | | | Low-cost patients | $ 8,153 | $ 3,618 | 3. Cost of CD correlated with cost of comorbidities | | | | | |
| | Women 2,893 | | | Men | $ 18,167 | | 4. 55% of all patients had comorbidities | | | | | |
| | Age ≤ 20 y 587 | | | Women | $ 18,999 | | | | | | | |
| | Age > 20 y 4,503 | | | Age ≤ 20 y | $ 22,796 | | | | | | | |
| | | | | Age > 20 y | $ 18,095 | | | | | | | |
| | | | | Age 11-20 y | $ 23,409 | | | | | | | |
| | | | | Age 21-30 y | $ 18,946 | | | | | | | |
| | | | | Age 31-40 y | $ 16,628 | | | | | | | |
| | | | | Age 41-50 y | $ 18,343 | | | | | | | |
| | | | | Age 51-60 y | $ 19,151 | | | | | | | |
| | | | | Age 61-70 y | $ 16,814 | | | | | | | |
| | | | | Age 71-80 y | $ 19,237 | | | | | | | |
| Park, 2020 | USA, northeast, southeast, mid-west, south.<br>Prevalent cases. Mean age ± 18y.<br>White 72%.<br>Urban 84%. | 2007-2016 | Pharmacy and administrative databases, Optum database.<br>Commercial insurance 85%, Medicare 15%.<br>Minimum insurance coverage 24 months.<br>Retrospective.<br>Patient co-payments partly included. | **IBD:** | | | 1. Data extrapolated from graphs. | Human capital approach.<br>Average wage derived from Bureau of Labour Statistics. | IBD | | | IBD patients lost more in earnings than controls. |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CD 23,720 | | | 2008 | $ 22,000 | | 2. Predictors of higher costs: Age <18 y, >65 y, biologics, diagnosis CD. | | Loss of wages | $ 3,000 | | |
| | UC 29,062 | | | 2016 | $ 30,000 | | | | Out-of-pocket expenses | $ 2,213 | | |
| | | | | **CD:** | | | | | | | | |
| | | | | Year 1 | $ 30,000 | | | | | | | |
| | | | | Year 10 | $ 38,000 | | | | | | | |
| | | | | **UC:** | | | | | | | | |
| | | | | Year 1 | $ 25,000 | | | | | | | |
| | | | | Year 10 | $ 15,000 | | | | | | | |
| Cohen, 2015 | USA. Working-age persons 18-64 y. | 2005-2013 | OptumHealth Reporting and Insights claims database. | **UC all cases:** | | | | Human capital approach. Equal number of matched non-IBD workers aged 18-64 y. Comorbidities included. | UC all cases: | | | 1.Direct costs greatly exceeded indirect costs in UC |
| | UC all cases 4,314 | | | Total direct | $ 15,378 | | | | Total indirect costs | $ 4,125 | | 2.Indirect costs higher in UC than controls |
| | Controls 4,314 | | | Hospitalization | $ 4,078 | | | | Disability | $ 1,727 | | |
| | UC moderate-severe 1,728 | | | Outpatients | $ 6,861 | | | | Absenteeism | $ 2,376 | | |
| | Controls 1,728 | | | Medication | $ 4,063 | | | | Controls | | | |
| | | | | **UC moderate-severe:** | | | | | Total indirect costs | $ 1,961 | | |
| | | | | Total direct | $ 22,874 | | | | Disability | $ 829 | | |
| | | | | Hospitalization | $ 7,357 | | | | Absenteeism | $ 1,082 | | |
| | | | | Outpatients | $ 9,245 | | | | UC moderate-severe: | | | |
| | | | | Medication | $ 5,741 | | | | Total indirect costs | $ 5,666 | | |
| | | | | | | | | | Disability | $ 2,713 | | |
| | | | | | | | | | Absenteeism | $ 3,071 | | |
| | | | | | | | | | **Controls** | | | |
| | | | | | | | | | Total indirect costs | $ 1,960 | | |
| | | | | | | | | | Disability | $ 772 | | |
| | | | | | | | | | Absenteeism | $ 1128 | | |
| Pilon, 2020 | USA. Working aged persons 18-64 y | 1999-2017 | OptumHealth Reporting and Insights claims database | Medical and pharmacy cost | | | | Human capital approach. Comorbidities included. | Disability and absenteeism | | | 1.Direct health care costs higher in UC than controls |
| | UC all cases 9,353 | | | **UC all:** | $ 18,198 | | | | UC all: | $ 5,307 | | 2.Indirect costs higher in UC than controls, and much higher in selected UC subgroups. Absenteeism |

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| | | | | | | | | | | | | driven mostly by visits to physicians |
| | Controls 46,765 | | | **Controls:** | $ 7,170 | | | | Controls: | $ 3,165 | | 3. Opioids used in 68% of UC |
| | | | | | | | | | UC subgroups: | | | |
| | | | | | | | | | UC surgery | $ 17,343 | | |
| | | | | | | | | | UC on opiates | $ 18,591 | | |
| | | | | | | | | | UC biologics | $ 11,898 | | |
| | | | | | | | | | UC depression | $ 8,640 | | |
| | | | | | | | | | UC moderate-severe | $ 9720 | | |
| Froes, 2018 | Brazil, nation-wide study. Prevalent cases. US$. | 2010 – 2014 | National Institute of Social security | | | | | | Disability pension: | | | 1. Data reported per year, mean year cost given |
| | IBD 15,277. | | | | | | | | Temporary | | | 2. Benefits higher in CD than UC |
| | | | | | | | | | CD | $ 3,221 | | 3. Both types of benefits tended to fall between 2010 and 2014 |
| | | | | | | | | | UC | $ 2,706 | | |
| | | | | | | | | | Permanent | | | |
| | | | | | | | | | CD | $ 5,698 | | |
| | | | | | | | | | UC | $ 5,077 | | |
| Froes, 2020 | Brazil, State of Rio de Janeiro. US$. | 2010-2018 | National Institute of Social Security | All prevalent cases | | | | | Disability pension cost: | | | |
| | CD 4,498 | | | | | | | | Temporary | $ 3,340 | | |
| | | | | | | | | | Permanent | $ 6,638 | | |

UC, ulcerative colitis; CD, Crohn's disease

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