

Inflammatory bowel disease (IBD) is a complex disease that health systems and managed care organizations have increasingly been reviewing to ensure effective health outcomes are being realized. Key stakeholders have recognized the potential importance of considering system-wide changes, leading to the recently formed GI Health Foundation (GIHF) Managed Care Coalition, an expert group composed of individuals with expertise in IBD, public health, health outcomes, health systems, pharmacoeconomics, and managed care. The GIHF Managed Care Coalition met at the 2022 Gi ReConnect Conference to review the “Impact of IBD on Healthcare Systems,” holding a two-hour state-of-the-art symposium followed by a two-hour advisory meeting, to address current issues in the management of IBD and its impact on healthcare systems from a managed care perspective.

The following lectures were first presented at the symposium (available at [gihealthfoundation.org](http://gihealthfoundation.org)):

<b>Overview of IBD: Epidemiology and Natural History</b>	<b>Bruce E. Sands, MD, MS</b> Chief of the Dr. Henry D. Janowitz Division of Gastroenterology Dr. Burrill B. Crohn Professor of Medicine Icahn School of Medicine at Mount Sinai Mount Sinai Health System New York City, NY	<b>Gaps Between Evidence and Practice in IBD</b>	<b>Gary R. Lichtenstein, MD</b> Professor of Medicine University of Pennsylvania School of Medicine Director, Center for IBD University of Pennsylvania Health System Philadelphia, PA
<b>Pharmacoeconomic Impact and Burden of IBD</b>	<b>Brennan Spiegel, MD, MSHS</b> Professor of Medicine and Public Health Director of Health Services Research, Cedars-Sinai Director, Master’s Degree Program in Health Delivery Science Cedars-Sinai Site Director, Clinical and Translational Science Institute (CTSI) Los Angeles, CA	<b>Challenges in IBD for the Community Gastroenterologist</b>	<b>Douglas C. Wolf, MD</b> Director, IBD Research Atlanta Gastroenterology Associates Atlanta, GA
<b>Chronic Care Management Approaches and Preventing Complications in IBD</b>	<b>David T. Rubin, MD</b> Joseph B. Kirsner Professor of Medicine Chief, Section of Gastroenterology, Hepatology and Nutrition Co-Director, Digestive Diseases Center University of Chicago Medicine Chicago, IL	<b>IBD Quality Indicators for the Practicing Healthcare Provider</b>	<b>Bruce E. Sands, MD, MS</b> Chief of the Dr. Henry D. Janowitz Division of Gastroenterology Dr. Burrill B. Crohn Professor of Medicine Icahn School of Medicine at Mount Sinai Mount Sinai Health System New York City, NY

Following the lectures, an advisory committee meeting took place, which was moderated by Gary Lichtenstein, MD, and Randy Ross, Vice President at Managed Market Resources (MMR). During this two-hour session, discussion ensued regarding the key obstacles and potential solutions in bettering the health outcomes for patients with IBD, as well as increasing the overall cost effectiveness for payers. The following stakeholders attended the presentations and participated in this advisory committee meeting:

- **Jeffrey Dunn, PharmD, MBA**, Chief Clinical Officer, Cooperative Benefits Group (CBG)
  - ◊ CBG is an infrastructure company that provides pharmacy benefit manager (PBM) and clinical pharmacy services to businesses (employer groups/coalitions and health plans/systems).
- **Eduardo Kneler, MD**, Medical Consultant, Department of Health Care Services, State of California
  - ◊ The Department of Health Care Services represents 14 million Medicaid lives in the state of California.
- **Marcelo Kugelmas, MD**, Director of Hepatology and Research, South Denver Gastroenterology
- **Daniel Kus, RPh**, Vice President, Pharmacy Services, Henry Ford Health System
  - ◊ The Henry Ford health plan covers more than 570,000 lives across all lines of business.
- **Myla Maloney, MBA, BCMAS**, Chief Commercial Officer, Applied Sciences, Premier Inc.
  - ◊ Premier Applied Sciences represents 4,400 hospitals and health systems and 225,000 non-acute sites.
- **Vishal Patel, MD**, Mission Hospitalist Consulting Service, Inpatient Medicine, St. Joseph Health
  - ◊ The service is part of a health system that covers approximately 1.9 million lives.
- **Ralph J. Riello III, PharmD, BCPS**, Clinical Pharmacy Specialist, Clinical & Translational Research, Yale University School of Medicine
  - ◊ Yale delivers advanced care in more than 100 subspecialties and averages 2.6 million patient encounters annually.

## Symposium Presentation Summary

### Impact of IBD on Healthcare Systems

Bruce E. Sands, MD, MS, discussed the natural course of Crohn's disease and ulcerative colitis (UC), collectively known as inflammatory bowel disease, or IBD. The prevalence of IBD is estimated to be 0.5% in the United States,<sup>1</sup> although, as Dr. Sands pointed out, no unified surveillance system for IBD currently exists in the US. Crohn's disease is highly active in roughly 80% of patients over the first year,<sup>2</sup> and in UC, the number is closer to 90%.<sup>3</sup> While 40% to 50% of patients achieve remission, a substantial number will continue to suffer from highly active disease or, in UC, require colectomy. Dr. Sands pointed out the chronic burden of Crohn's disease (Figure 1). Over a period of several years, the cumulative probability of inflammation gives way to strictures and penetrating lesions.<sup>5</sup> These data support what would become a theme in the symposium, that early diagnosis and treatment of patients with IBD can improve outcomes and potentially reduce costs.

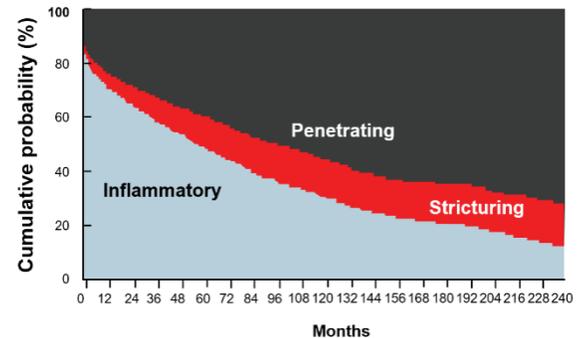


Figure 1. The Evolution of Crohn's Disease

Brennan Spiegel, MD, MSHS, picked up on this theme in his presentation, titled "Pharmacoeconomic Impact and Burden of IBD." Dr. Spiegel reviewed the highly useful concept of ICER, or incremental cost-effectiveness ratio. Simply stated, ICER is the change in the cost in something divided by the change in the effect. ICER is considered alongside another useful acronym, QALY, or quality-adjusted life year. Certain interventions are actually cost saving, such as immunizations, while IV proton-pump inhibitors for bleeding ulcers, Dr. Spiegel pointed out, are associated with a cost per QALY ICER of over \$700,000. He cited the systematic review by Drs. Huoponen and Blom, stating, "With a threshold of 35,000 €/QALY, biologics seem to be cost-effective for the induction treatment of active and severe inflammatory bowel disease."<sup>6</sup> This cost-effectiveness seems to be borne out by more recent studies.<sup>7,8</sup>

David T. Rubin, MD, noted that IBD outcomes are improving for a variety of reasons, including improvements in therapies, improvements in management goals, better evidence, and even changes in the natural history of IBD. With newer therapies, Dr. Rubin pointed out, patients are able to achieve more stable disease control and deeper levels of remission, such as mucosal healing. Improved outcomes are also due to increased emphasis on steroid-free care and a movement in the field from reactive management to proactive management.

To support these assertions, Dr. Rubin picked up on the theme of early detection and intervention by highlighting some key data. Specifically, he presented evidence that earlier, or "top-down," use of anti-TNF therapy in Crohn's disease lowers the risk of concomitant corticosteroid use, reduces the need to escalate the dose of anti-TNF agents or to discontinue or switch anti-TNF therapy, and reduces the number of Crohn's disease-related surgeries (Figure 2).<sup>9</sup> Likewise, early initiation of biologics in Crohn's disease reduces ER visits and hospitalizations.<sup>10</sup>

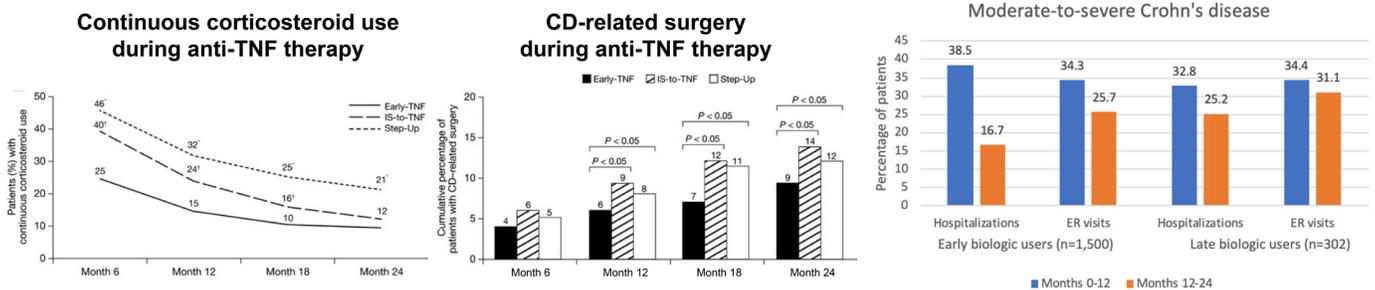


Figure 2. Earlier Use of Anti-TNF Biologic Therapy in Crohn's Disease Has Better Outcomes<sup>9,10</sup>

Similarly, patients with UC who achieved mucosal healing from infliximab treatment are less likely to need colectomy.<sup>11</sup>

One important concept that emerged from Dr. Rubin's talk was the importance and potential benefit of therapeutic drug monitoring (TDM). It is not ideal to assess serum concentrations of anti-TNF when the patient begins to experience symptoms; rather, periodic, proactive disease and drug assessments should be performed to detect presymptomatic issues and provide lead time for interventions to prevent complications. Sustained disease control without worsening symptoms is substantially higher in patients who undergo TDM compared with standard therapy (Figure 3).<sup>12</sup>

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Figure 3. Time to Disease Worsening

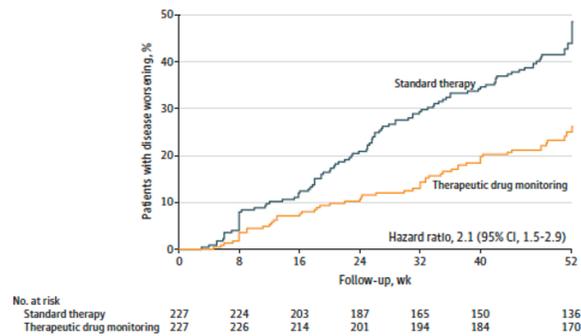


Figure 3. TDM Is Superior to Standard Reactive Therapy

Dr. Rubin also provided an approach to IBD management that incorporates proactive monitoring and objective treatment targets (Figure 4).

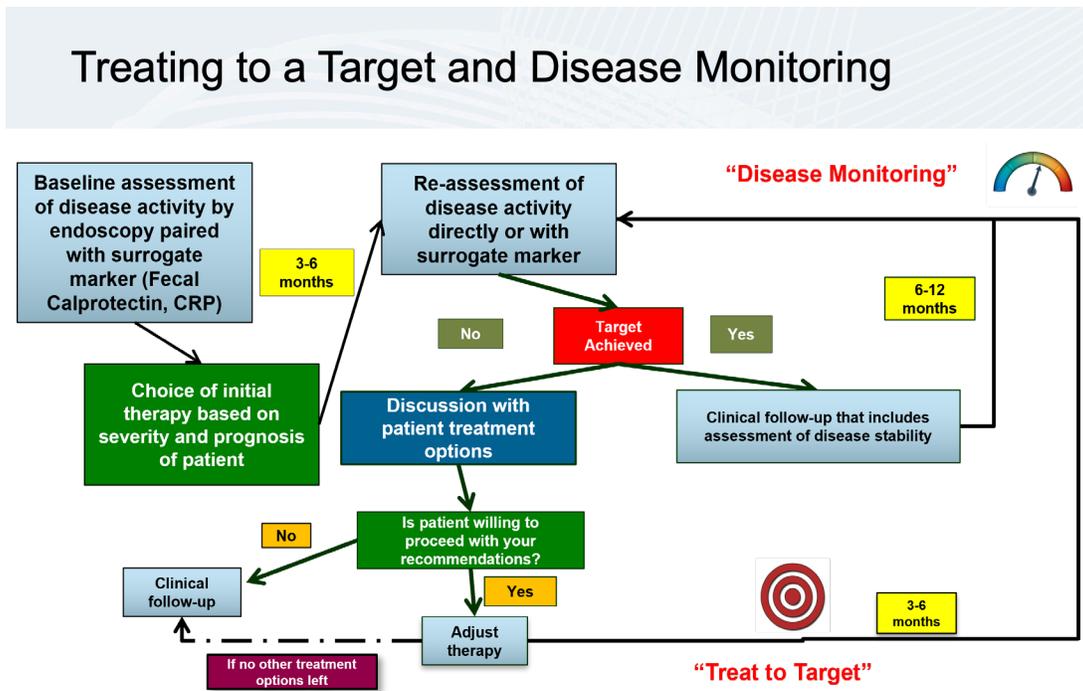


Figure 4. Treating to a Target and Disease Monitoring.

Lastly, Dr. Rubin discussed the present and near-future state of IBD monitoring. Currently, clinicians use a combination of patient-reported symptom assessment, endoscopic assessment, biomarkers, and TDM to get a subjective and objective picture of a patient’s status.<sup>13</sup> In the near future, point-of-care and at-home testing that includes passive biosensors and predictive therapeutic biomarkers will extend proactive therapeutic monitoring to near real-time.<sup>14</sup>

While the care of patients with IBD has improved over the last two decades, gaps between evidence and practice remain, as detailed by Gary R. Lichtenstein, MD. Thus, as outcomes have clearly improved, real-world implementation of lessons learned can still be improved. Dr. Lichtenstein reminded the group that virtually all patients with Crohn’s have clinically significant inflammation at presentation and roughly half will develop an intestinal complication within 20 years of diagnosis.<sup>15</sup> Likewise, ≈50% of patients will develop steroid dependence or resistance, ≈80% require hospitalization during the disease course, and the 10-year risk of major abdominal surgery is between 30% and 55%.<sup>15</sup> Dr. Lichtenstein reiterated the apparent benefits of TDM that other presenters had mentioned, citing improved outcomes with vedolizumab TDM in the GEMINI trials<sup>16-18</sup> and therapeutic monitoring of ustekinumab in the UNITI trials.<sup>19,20</sup>

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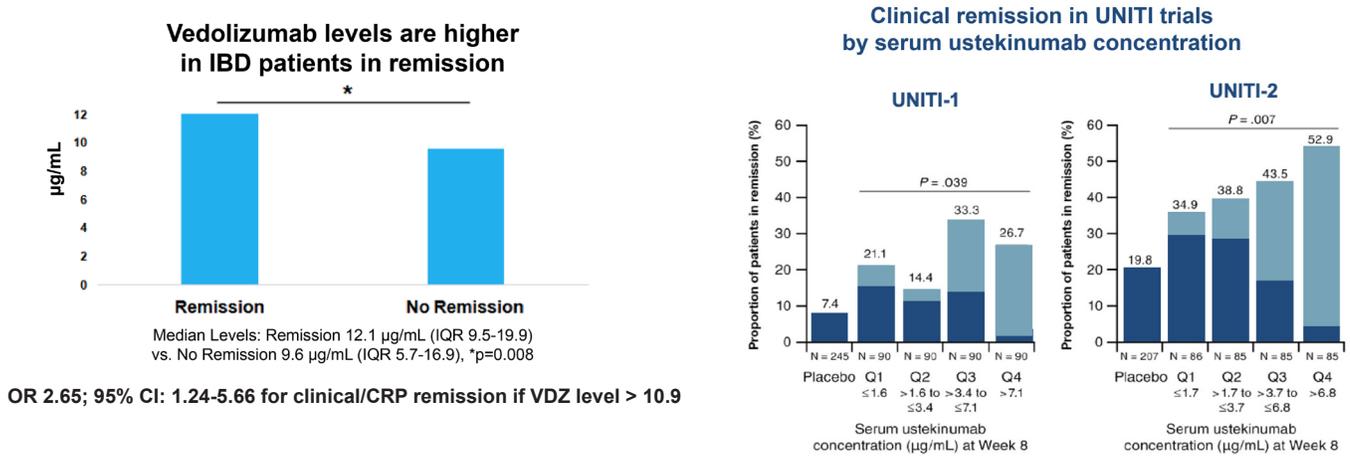


Figure 5. Higher Levels of Biologic Associated with Remission Rates

However, he did acknowledge that large, randomized, prospective, placebo-controlled trials are not now and will never be feasible, so Dr. Lichtenstein suggested that real-world results and good clinical judgment are sufficient to support the routine use of TDM in patients with IBD. He noted TDM allows clinicians to manage biologic treatment to achieve the greatest clinical benefit and the fewest adverse sequelae. Indeed, the first biologic—given as early as possible—provides the best opportunity for long-term remission and minimal disease progression.<sup>21</sup> Moreover, higher drug levels without anti-biologic antibody formation are associated with better remission rates and better rates of mucosal healing.<sup>21</sup> By proactively assessing biologic agent levels, clinicians may avoid inadequate dosages or inappropriate drug classes and decrease the risk of antibody positivity.

Dr. Lichtenstein also pointed out the gaps that still exist for treated patients in specific populations, namely pregnant women, the elderly, and those with prior malignancy. The 2021 results from the PIANO registry suggests withholding treatment permits uncontrolled inflammatory disease, which is riskier to the mothers and fetuses than biologic treatment itself. Therefore it is not recommended to withhold biologic treatment during pregnancy. Drug exposure did not increase the rate of congenital malformations, spontaneous abortions, preterm birth, low birth weight, or infections during first year of life.<sup>22</sup> Conversely, spontaneous abortion before 20 weeks was independently associated with active disease (HR 3.41; 95% CI 1.51-7.69) and prior spontaneous abortion (HR 2.17; 95% CI 1.05-4.49).<sup>22</sup> While drug treatment did not increase the rate of preterm birth or infections, preterm birth was associated with increased infant infection (OR 1.73; 95% CI 1.19-2.51), suggesting that preterm birth is more likely to lead to infection than is IBD drug treatment. A meta-analysis of 28 clinical studies revealed active IBD at conception and pregnancy is associated with an increased risk of adverse pregnancy outcomes.<sup>23</sup>

IBD treatment in elderly patients or those with a history of cancer poses a greater clinical challenge, according to Dr. Lichtenstein's presentation. A meta-analysis that included 14 unique studies comprising 4,719 older users of biologics, 13,305 younger users of biologics, and 3,961 older patients who did not use biologics showed that older users of biologic agents have an increased risk of infections compared with younger users or older patients who do not use biologics.<sup>24</sup> Specifically, older users of biologics had a three-fold increase in risk of infection compared with patients who did not use biologics (OR 3.60; 95% CI 1.62-8.01).<sup>24</sup> Thus, a more nuanced approach to care is needed, one that considers risk factors in elderly IBD patients, including immunosenescence, frailty, and severity and extent of disease, among others. Larger prospective studies are needed to define a clear treatment path for patients with prior malignancy.

Douglas C. Wolf, MD, a gastroenterologist working in private practice, highlighted some of the challenges faced by specialists in the community. In many ways, Dr. Wolf pointed out, challenges that community GI specialists face mirror those in academic institutions. Both practice venues face the challenges of delayed diagnosis and may prescribe from the same set of treatment options. However, management team composition and patient access to treatment are different between the two settings. For instance, Dr. Wolf noted, the medication approval process is more challenging in community practice. There are clear differences in academic or hospital pharmacies compared with community or specialty pharmacies. In an online survey of patients with UC or Crohn's disease, 68% (n=757) of patients reported a delay in diagnosis. The perceived reasons for delay varied, but access to care apparently contributed (Figure 6). Moreover, diagnostic delay leads to significantly worse outcomes (Table 1).

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Diagnostic delay is not the only barrier to effective treatment among IBD patients in the community, according to Dr. Wolf. The FDA-approved biologic dosing regimen is critical to its effectiveness, and in patients with refractory disease, dose escalation may be required. The proverbial stars must align for this to be realized, however. Dr. Wolf noted insurance approval issues, delays, and denial may delay or prevent care. Biologic dosing is higher in IBD than it is for other immunologic disorders, such as rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, and uveitis—perhaps as much as two-fold higher in IBD. This alone can lead to incorrect approvals or delays. Dr. Wolf also observed that patient factors are certainly at play, too. Financial issues, scheduling challenges, and delays in pre-biologic treatment testing (e.g., TB) create delays and lapses in treatment that decrease therapeutic drug levels and increase the risk for antibody formation.

Intestinal stenosis	p=0.008
Perianal fistula	p=0.020
Internal fistula	p=0.012
Any fistula	p=0.001
Resection surgery	p=0.070
Fistula surgery	p<0.001
Any complication	p=0.001

### Perceived reasons for delay

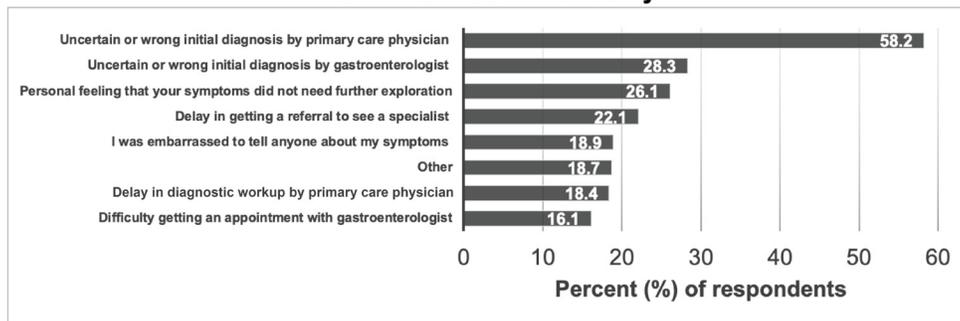


Figure 6. Perceived Reasons for Diagnostic Delay

Bruce E. Sands, MD, MS, bookended the presentation by offering practical guidance for assessing and assuring quality in IBD management. Dr. Sands argued that variation in care reflects lower quality of care; and indeed, variability in care is a surrogate for inferior care.<sup>26</sup> Variability in care may manifest as overuse of the emergency department for routine care, underuse of steroid-sparing therapy, or misuse of colonoscopy, for example. Dr. Sands chose to focus on three care processes that perhaps represent the low-hanging fruit to increase standardization in IBD care: prioritizing steroid-sparing therapy, providing venous thromboembolism (VTE) prophylaxis, and testing for *C. difficile* infection during inpatient stays. Published data strongly support each of these positions, but practice gaps remain. For example, steroid use doubles the risk of mortality and the number needed to harm is only 4.<sup>27,28</sup> However, in 60% of patients hospitalized for IBD, no attempt was made to transition to steroid-sparing therapy (Figure 7).<sup>4</sup>

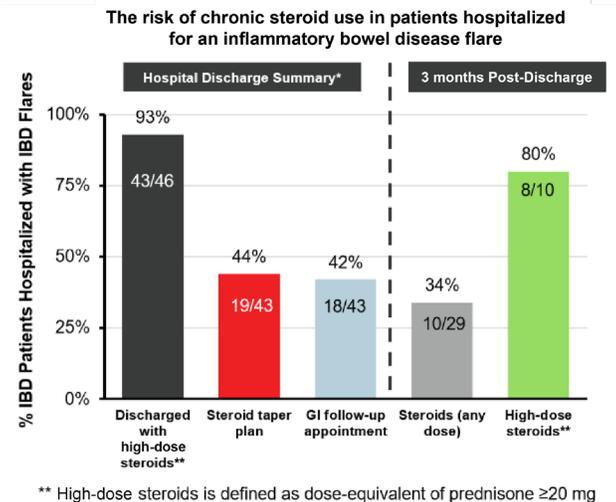


Figure 7. Steroids Prescribed During Inpatient Stay Tend to Persist after Discharge<sup>4</sup>

In another example, VTE<sup>29</sup> has been shown to be substantially more common in patients with IBD, yet 29.1% of gastroenterologists are unaware that VTE prophylaxis is recommended for patients hospitalized with IBD flares without severe bleeding. *C. difficile* is also much more common in IBD patients,<sup>30</sup> yet detection and treatment are lacking.

In an effort to improve the consistency and standardization of care, Dr. Wolf pointed to helpful resources published by Cornerstones Health and the Crohn's & Colitis Foundation. Each group provides a checklist that helps providers track the various quality-of-care indicators needed in patients with IBD. Cornerstones Health offers the IBD Checklist for Monitoring & Prevention™, which tracks immunizations, therapy-related testing, bone-health indices, and cancer prevention, among others. The Health Maintenance Checklist for Adult IBD Patients by the Crohn's & Colitis Foundation provides a similar care-tracking system. Consistently implementing these regimens of care could reduce variability and increase quality of care.

## Advisory Committee Meeting Summary

### IBD Medication Cost Is Ever-Increasing, but Cost Control Is Possible

A central issue throughout the advisory panel discussion was how to provide patients with advanced IBD therapies while containing costs to payers and patients. Jeffrey Dunn, PharmD, MBA, stated that the cost of prescriptions has increased from 9% of total healthcare spending to 23% over the past several years. Moreover, drug costs double every three to four years. Employers have few ways to contain costs, namely increase deductibles, increase premiums, or add co-insurance. Better alignment between pharma, payers, and clinicians could improve patient care and reduce costs throughout the healthcare system.

Both payers and clinicians agreed that patients should be switched to biosimilars more often than they are today. Data indicate that switching from Remicade to the infliximab biosimilar, for example, is safe and effective. The clinicians on the panel admitted that there remains some resistance to biosimilars from patients, patient advocacy groups, and even some providers. However, the panelists did state that thought leaders in IBD care, the physician panelists themselves, including Bruce Sands, MD, MS, and Gary R. Lichtenstein, MD, have embraced the regulatory pathway for biosimilars, have adopted them into their own practices, and have published editorials supporting biosimilar use.

The panelists generally agreed that the “cost-effectiveness” needs applied routinely and thoughtfully in IBD care. Indeed, “comparative cost-effectiveness” should be increasingly considered. Dr. Dunn posited that if doubling the dose of a medication doubles the cost but only improves disease control by 5%, the higher dose should not be considered equally cost-effective as the lower dose. Dr. Sands agreed that blind dose escalation is not appropriate; however, relatively expensive dose increases may be justified in specific patients with specific disease biology. In other words, in select patients, doubling the dose may result in 50% improvement rather than 5% and, thus, be justified. Clinicians, he argued, must be trusted to make these decisions but also be held accountable for demonstrating effectiveness through objective means, such as colonoscopy and disease biomarkers.

#### Potential Opportunities

Costs in IBD care are rising, especially the costs of advanced therapeutics. Advisory board members identified some possible opportunities to decrease costs:

- Further increasing adoption of biosimilars can substantially reduce costs. This can perhaps be accomplished through patient and provider education/awareness efforts.
- Healthcare economists should consider comparative cost-effectiveness when evaluating IBD therapies.

### Collaborative Care between Pharma, Payers, and Clinicians Can Improve Patient Care and Reduce Costs

Approval denials have been and remain a significant barrier to care. Currently, dominant treatments like advanced therapies are third or fourth line in terms of reimbursement and even FDA prescribing guidelines. The FDA approves therapies based on safety, followed by efficacy, and tilts towards the lowest effective dose. Thus, FDA guidelines do not always allow individualized dosing, and payer reimbursement decisions should not be made solely on these recommendations.

The implication is that authorizing dominant treatments without requiring failure of dominated therapies ultimately represents a cost savings and provides better patient care. While the preceding presentations showed the financial and health burdens caused by delaying advanced therapies in appropriate patients, Douglas Wolf, MD, stated that a delay in reauthorization is often far worse than a delay in initial authorization. Patients who are doing well on an advanced therapy may develop antibodies if they have to wait two to four weeks for reauthorization.

On the other hand, participants generally agreed that reimbursement approval should be contingent on setting a treatment goal, and reauthorization decisions should be at least partially based on monitoring, meeting, and maintaining that goal. Advanced therapies do not need to be continued indefinitely if they are not objectively effective, in other words. David Rubin, MD, stated that initially, clinicians were thrilled when a drug finally worked, driving them to continue therapy as long as they could. Today, more options exist to tailor therapy based on outcomes.

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Thus, Dr. Rubin acknowledged that some proof of benefit should be required for reauthorization. Moreover, as additional insights on induction and maintenance are revealed, these could and should be integrated into both workflows and approval processes.

### Potential Opportunities

- Effective collaboration for reauthorization could greatly improve patient care and prevent treatment resistance.
- Set a treatment goal, such as sustained remission, before starting an advanced treatment.
  - ◇ Adapting the recommended management guidelines for IBD through a health outcomes/pharmacoeconomic lens may enable providers and payers to more effectively communicate and thus more efficiently manage their IBD patients.

### Integrating Advanced IBD Treatments into the EMR Could Improve Patient Care and Outcomes

Myla Maloney, MBA, BCMAS, identified a theme across the day's presentations that outcomes are better if patients are treated with advanced therapies earlier than indications would typically permit. She mentioned that various studies analyzing insurance-claim data show that early IBD care actually reduces the total cost of care because it reduces expensive complications and comorbidities. Yet, despite these studies, clinicians are still not prescribing advanced therapies early in the disease process. Ms. Maloney suggested that clinicians may be more comfortable prescribing these therapies earlier, and CFOs of large health systems may be more inclined to pay for them, if they were presented with data collected from real-world practice rather than simply billing and claims data. These studies, with the help of artificial intelligence and machine learning, are what Premier Applied Sciences specializes in designing and conducting.

This concept was well-received by the group, including by Bruce Sands, MD, MS. Dr. Sands named two pain points for prescribing physicians: one, the perceived or real barriers to getting the advanced therapy approved, and two, the fear of committing an error or being responsible for a complication from an advanced therapy. Earlier he had presented data suggesting gastroenterologists are more likely to delay or underdose therapy rather than "cause" a complication. Unfortunately, there is still a prevailing perception that these therapies are "big guns" with severe complications when the data clearly show that they are not only safe, but they are much safer than active disease.

In addition to early prescription, David Rubin, MD, drew attention to Dr. Sands' presentation on overtreatment. Specifically, how can stakeholders identify and eliminate therapies that are used excessively or when they're not providing additional benefit? Indeed, de-escalation of unhelpful or unnecessary therapies could also conserve IBD expenditures. A practical example was the presumably large number of providers who continue to prescribe 5-ASA medications after starting an advanced therapy. No compelling evidence supports continuing 5-ASAs after starting an advanced therapy, and some work indicates that it is safe to discontinue them. While 5-ASAs are comparatively inexpensive, if they are unnecessary, then discontinuing them on a national scale could be a substantial cost savings.

Most stakeholders on the advisory panel suggested that both overtreatment and undertreatment could potentially be reduced by integrating "nudges" into the electronic medical record (EMR). Clinicians could be made aware of instances in which patients could benefit from an early advanced therapy or other instances in which excessive therapy could be discontinued. Ralph J. Riello III, PharmD, BCPS, mentioned that EMR optimization has shown clear results in heart failure patients who could benefit from SGLT2 inhibitors, which are expensive. Placing an alert in the EMR workflow was tantamount to giving the providers permission to prescribe the drug. They assume there is a pharmacist who will help them navigate that process and smooth out issues on the payer side.

Dr. Riello mentioned two examples for IBD gleaned from the preceding talks. Many patients on long-term steroid therapy likely should not be, so alerting the provider via the EMR may be a way to raise the possibility of an alternate therapy. Similarly, prophylaxis against VTE is cost-effective and cuts the risk of recurrent VTE in half. A nudge from the EMR could increase the percentage of patients who receive this treatment.

### Potential Opportunities

- Clinicians should conduct studies that evaluate real-world practice data to show the efficacy, safety, and cost-effectiveness of early prescription of advanced therapies.
- Artificial intelligence and machine learning systems may be able to identify additional risk factors in IBD that would allow clinicians to further individualize patient care and justify the comparative cost-effectiveness to payers and healthcare systems.
- Payers should reimburse for dominant therapies over dominated therapies. Certain therapies, such as mesalamine for initial treatment of Crohn's, can and should be denied by payers outright. Other examples may exist and, if found, could improve care and reduce costs.

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