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aga American Gastroenterological Association

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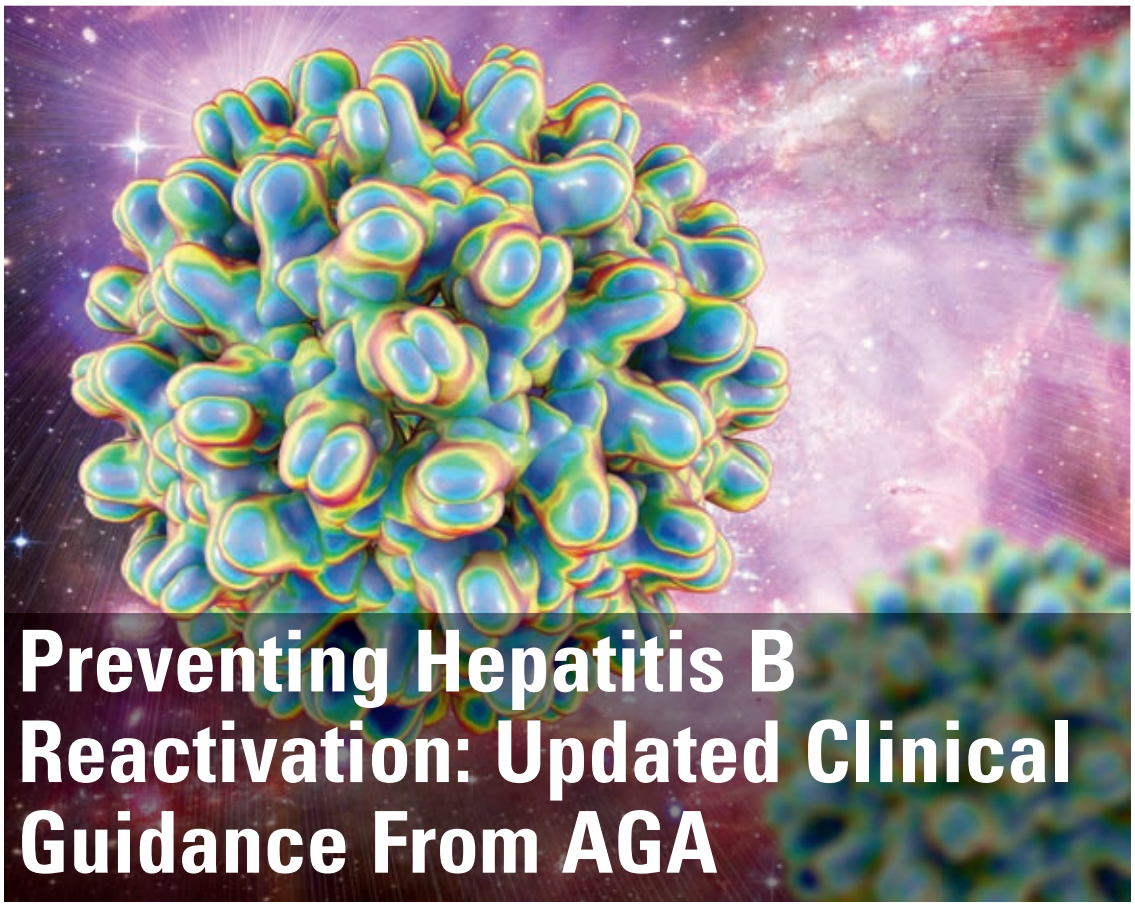

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Preventing Hepatitis B Reactivation: Updated Clinical Guidance From AGA

BY DIANA SWIFT

FROM GASTROENTEROLOGY

The American Gastroenterological Association (AGA) has released an updated clinical practice guideline on the prevention of hepatitis B virus reactivation (HBVr) in at-risk persons. The document was published in *Gastroenterology* (2025 Feb. doi: 10.1053/j.gastro.2024.11.008) and replaces a previous guideline on prophylaxis for immunosuppressed patients issued in 2014 (Gastroenterology. 2015 Jan;148[1]:215-219).

Since then, many novel classes of immunosuppressives have been approved for various conditions, and potentially immunosuppressive therapies such as transcatheter arterial chemoembolization have been recognized as relevant to potential HBVr.

With reactivation a risk after immune-modulating exposures, such as to multiple drug classes and disease states, the update provides frontline clinicians with evidence-based advice for the management of HBVr in vulnerable individuals. And while antiviral prophylaxis is recommended for many, in select cases careful clinical monitoring may suffice for risk management.

“The risk of HBV reactivation depends on

See **Reactivation** · *page 18*

Subcutaneous Guselkumab Proves Efficacious for IBD in Two Studies

BY BECKY MCCALL, MSC, MSCPH

FROM ECCO 2025

BERLIN — Induction therapy with subcutaneous guselkumab demonstrated significant efficacy in patients with moderately to severely active ulcerative colitis (UC), according to results from the phase 3, randomized, double-blind, placebo-controlled ASTRO study.

Importantly, the study also showed that subcutaneous induction is consistent with intravenous (IV) induction of guselkumab in UC.

“The flexibility of a fully subcutaneous treatment regimen would be a welcome option for many patients, especially those with busy and active lifestyles,” said study lead Laurent Peyrin-Biroulet, MD, head of the inflammatory bowel disease (IBD) unit at University Hospital of Nancy, France.

Peyrin-Biroulet presented the results at the European Crohn’s and Colitis Organisation (ECCO) 2025 Congress.

“I think it’s an evolution and improvement in terms of IBD management,” he said. “We are happy that our patients will have the choice.”

Guselkumab is a selective dual-acting interleukin (IL)–23p19 subunit inhibitor that potently blocks IL-23 and binds to CD64, a receptor on cells that produce IL-23, and is the only full subcutaneous IL-23 available. The drug is approved in some countries, including the United States, for UC.

The ASTRO Study

Building on data from the QUASAR studies, which

See **Guselkumab** · *page 23*

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LETTER FROM THE EDITOR

A Threat to Scientific Progress

The United States has long been recognized as a global leader in biomedical research and scientific discovery, with federal research and development (R&D) funding serving as the bedrock of national innovation. Substantial federal investment in biomedical research has stemmed from a recognition of its importance in fueling critical discoveries that improve patient care and the health of our communities.

In the United States, academic institutions play a key role in conducting research in the national interest and collaborating with industry, with most of the federal research funding distributed by the National Institutes of Health, National Science Foundation, and other agencies awarded to university-based academic investigators. In a 2014 report, the National Academies of Sciences, Engineering and Medicine identified three pillars of a highly productive research system: a talented and interconnected workforce, adequate and dependable resources, and world-class basic research in all major areas of science.

A series of recent, short-sighted federal policy decisions threaten the future of scientific discovery by eroding these pillars. Decisions to freeze previously awarded federal grant funding, delay grant review panels, fire federal scientists, and propose crippling cuts to indirect cost rates (among others) have sent shock waves through the research community and already have led some prominent research institutions to cut staff and divert resources away from groundbreaking research.

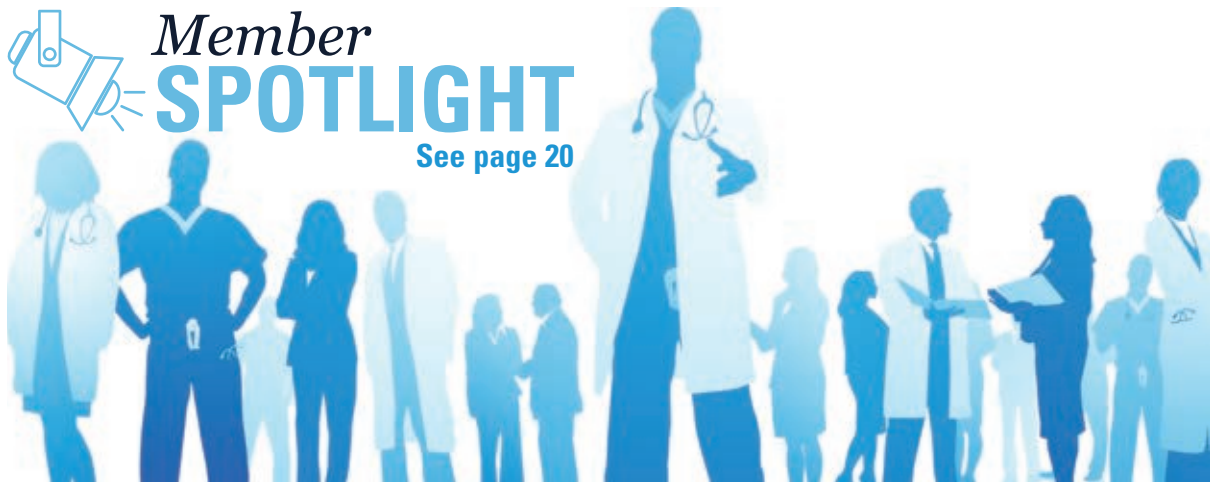
Dr. Adams

'If ever there was a time for advocacy to reinforce the critical link between biomedical research and downstream improvements in patient care and public health, it is now.'

While the acute effects of these changes are just beginning to be felt, it is the long-term effects of these decisions on future medical and scientific discovery that will be most devastating to society. If ever there was a time for advocacy to reinforce the critical link between biomedical research and downstream improvements in patient care and public health, it is now.

In our April issue, we highlight important research advancements in inflammatory bowel disease presented at February's Congress of the European Crohn's and Colitis Organisation (ECCO) in Berlin. In this month's Member Spotlight, Abigail Meyers, MPAS, PA-C, outlines her impactful work as a member of AGA's newly formed Nurse Practitioner and Physician Assistant Task Force and shares how her personal journey as a patient with inflammatory bowel disease allows her to be a more powerful advocate for important issues impacting other patients with this condition. ■

Megan A. Adams, MD, JD, MSc
Editor in Chief



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GI&Hepatology News

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Best Practices When Using POEM to Treat Achalasia: AGA Clinical Update

BY MEGAN BROOKS

FROM GASTROENTEROLOGY

The American Gastroenterological Association (AGA) has released a clinical practice update synthesizing current available evidence and expert opinion on peroral endoscopic myotomy (POEM) to treat achalasia and other esophageal motility disorders.

"Any patient suspected to have achalasia, or difficulty swallowing for that matter, should undergo a comprehensive diagnostic workup, and that should include clinical history, review of medication, as well as tests. The diagnosis should not be based on isolated tests but on the clinical picture as a whole," first author Dennis Yang, MD, AGAF, with the Center for Interventional Endoscopy, AdventHealth, Orlando, Florida, noted in an AGA podcast about the update.


Dr. Yang

The clinical practice update, published in *Gastroenterology* (2024 Oct. doi: 10.1053/j.gastro.2024.08.038), includes 12 "best practice advice" statements.

Since its introduction to clinical practice more than a decade ago, POEM has matured and gained widespread acceptance because of its efficacy and safety profile.

POEM has at least similar outcomes to laparoscopic Heller myotomy and pneumatic dilation for type I and type II achalasia with better results for those with type III achalasia, Yang noted.

"However, besides disease phenotype, we need to remember that choosing the right treatment for the patient is going to be based on multiple factors including patient characteristics as well as local expertise," Yang added.

In terms of technical considerations, the update states that both anterior and posterior tunnel approaches demonstrate comparable success and postprocedure reflux rates. Tunnel orientation should be tailored to the patient's surgical history and endoscopist's preference.

It further states that optimal length of the myotomy in the esophagus and cardia, as it pertains to treatment efficacy and risk for postprocedure reflux, remains to be determined.

Adjunct techniques, including real-time intraprocedure functional luminal impedance planimetry, may be considered to tailor or confirm the adequacy of the myotomy.

Same-day discharge after POEM can be considered in select patients who meet discharge criteria. Patients with advanced age, significant comorbidities, poor social support, and/or access to specialized care should be considered for hospital admission, irrespective of symptoms.

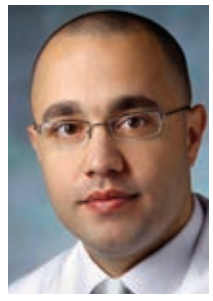
The update notes that specific guidelines on the role and extent of antibiotic prophylaxis before and after POEM are lacking. A single dose of antibiotics at the time of POEM "may be sufficient" for antibiotic prophylaxis.

In terms of immediate post-POEM care, the update notes that the clinical impact of routine esophagram or endoscopy immediately post POEM remains unclear. Testing can be considered based on local practice preferences and in cases in which intraprocedural events or postprocedural findings warrant further evaluation.

Proton pump inhibitors are recommended immediately following POEM, as gastroesophageal reflux disease (GERD) is common following POEM, occurring in up to 65% of cases.

Routine endoscopic surveillance is advised to monitor GERD, disease progression, and esophageal cancer risk, which is significantly higher in achalasia patients.

"Just like diabetes and hypertension, we need to remember that achalasia is a chronic disease and long-term postprocedural surveillance is strongly encouraged to monitor disease progression as well as potential complications of reflux," Yang said.


Dr. Khashab

He noted that surveillance should be considered irrespective of patient symptoms because many of these patients may remain asymptomatic.

"Primary gastroenterologists should have a very low threshold in referring the patient back to the POEM endoscopist or any specialized esophageal center because the ideology of symptoms in these patients can be quite difficult to tease out and often require comprehensive diagnostic workup," Yang said.

Evidence for POEM in esophagogastric outflow obstruction and other nonachalasia spastic motility disorders is limited and should be considered on a case-by-case basis only after other less invasive approaches have been exhausted, the update states.

For perspective on the POEM clinical practice update, this news organization spoke with Mouen Khashab, MD, director of therapeutic endoscopy, Johns Hopkins University, Baltimore.

"The document is very well written and comprehensive," Khashab said. He noted, however, that he would have liked to see greater emphasis on the value of a short myotomy in the esophagus and cardia.

"There is level I evidence that the short esophageal myotomy is equivalent to a long esophageal myotomy for type I and II achalasia. When you do a short myotomy, you save procedure time and there is potentially a lower incidence of blown-out myotomy," he said.

This research had no commercial funding. Yang serves as a consultant for Boston Scientific, Olympus, FujiFilm, Microtech, Medtronic, 3D-Matrix, and Neptune Medical, and has received research support from Microtech and 3D-Matrix. Khashab had no relevant disclosures.

The Federal Trade Commission's Non-Compete Ban

What Is It, What Is Its Status Today, and What Is Its Future?

BY TIMOTHY CRAIG ALLEN, MD, JD

Non-compete agreements (NCAs) in physician contracts, also termed "restrictive covenants" or "covenants not to compete," have become a hot topic recently because of the Federal Trade Commission's (FTC's) April 2024 ruling invalidating almost all NCAs. But in fact, NCAs have long been controversial, and no more so than in the realm of physician NCAs, which involve substantial policy concerns.

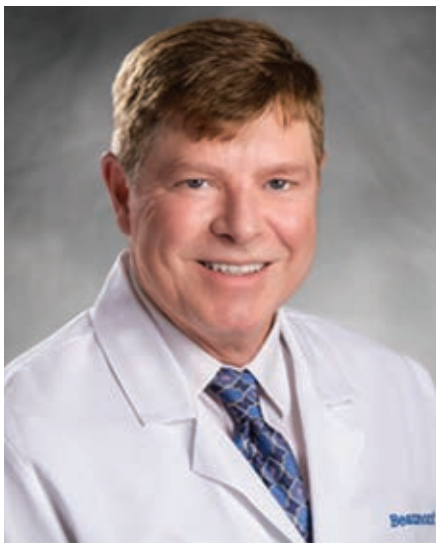
Given the intricacies and importance of NCAs, and the fact that up to 45% of physicians currently have contracts containing NCAs, it behooves physicians to understand the foundation of the NCA, how it relates to a physician employment contract currently, and its possible evolution.

What Is It?

Generally speaking, an NCA, usually in the form of an employment contract clause, is an agreement between the employer and the employee that the employee will not enter into post-contract competition with that employer within the limitations of a specific duration, scope of practice, and/or geography. NCAs have traditionally been regulated under state statutory law and common law and have been permitted based on policy considerations that attempt to balance competing employee and employer interests. Physicians should understand their states' statutory treatment of an NCA.

NCAs protect important employer business interests, including protecting proprietary information, safeguarding trade secrets, reducing employee turnover, and protecting patient lists. Employees, though, have limited mobility in changing professional positions, have less bargaining power with the employer, and may find themselves with limited options for comparable professional positions.

The NCA ostensibly appears to greatly benefit the employer's interests over the employee's; however, NCA protection of employer interests may also substantially benefit employees by encouraging substantial employer investment in employees whom the employer



Courtesy College of American Pathologists

Dr. Allen

recognizes as a stable and likely long-term human resource, ultimately fostering increased employee satisfaction and innovation. Indeed, one concern with the FTC's non-compete ban is the potential for significant underinvestment in information sharing and employee training, because employers would, without a NCA, be less likely to recoup those employee investments and would have limited ability to keep competitors from free-riding on investments in employees who leave and join competitors. Ultimately, this would lead to decreased market efficiency.

What Is Its Status Today?

Regulation of NCAs, including physician NCAs, has traditionally been based on state statutory law and common law. Perhaps because of the increasing use of the NCA in professional settings, the NCA has been increasingly scrutinized by courts and state legislatures in the last few decades, with an overall increasing focus on NCA reasonableness and appropriate fit in individual employment settings, and with an emphasis on employer demonstration of legitimate and significant business interests for using a NCA.

States have evolved differently in their treatment of NCAs; some states ban NCAs altogether while others allow them with varying interpretation and enforceability, frequently focused upon the NCA's duration, scope, and geography. Similarly, in common law, courts will frequently invalidate NCAs that are found to be unreasonably overbroad, either geographically, temporally, and/or in regard to scope.

On April 23, 2024, however, the FTC altered this existing state of affairs by issuing a rule banning new NCAs in all employment situations after September 3, 2024. The rule also holds that existing NCAs are not enforceable, with a small carveout for some senior executives. It applies to for-profit businesses, and some, but not all, non-profit organizations. The FTC's stated intent is to reduce healthcare spending by increasing employee compensation and mobility. The FTC's ban is likely meant to reduce transaction costs by increasing physician mobility.

There have been several lawsuits regarding the FTC ruling, challenging it on different grounds. The US District Court for the Northern District of Texas in *Ryan LLC v FTC* issued first a preliminary injunction, then a final decision overturning the FTC's rule. The Court held that the FTC had exceeded its statutory authority, and further, that the rule was arbitrary and capricious. It noted that the rule's "categorical ban" has no equivalent in state law, is "unreasonably overbroad without a reasonable explanation," "provides no evidence or reasoned basis," does not "consider the positive benefits of non-compete agreements," and does not "address alternatives to the Rule." The *Ryan* Court reasoned that as an administrative agency, the FTC can act only as Congress authorizes by statute. On October 18, 2024, the FTC appealed the Court's decision to the Fifth Circuit Court of Appeals, seeking to reverse the holding setting aside its NCA ban.

The United States District Court for the Eastern District of Pennsylvania in *ATS Tree Services LLC v FTC* denied the plaintiff's motion to stay enforcement of the rule, refusing to issue a preliminary injunction preventing its implementation. As in *Ryan*, the *ATS Tree Services LLC v FTC* plaintiffs argued that the FTC had exceeded its statutory authority in issuing the rule. However, the Plaintiff did not appeal the holding.

The US District Court for the Middle District of Florida in *Properties of the Villages, Inc v FTC* held, like *Ryan*, that the rule exceeds the FTC's statutory authority, noting the FTC's prior lack of any NCA enforcement actions; however, its reasoning differed from *Ryan*. The Florida Court held that the FTC in fact has statutory authority to issue such rules; however, the Court held that the FTC could not enforce its rule because it violates the "major questions doctrine." The "major questions doctrine" requires an agency such as the FTC to "point to clear congressional authorization" for any rule it issues that has "extraordinary ... economic and political significance," as the NCA ban rule certainly does.

What Is Its Future?

The FTC's NCA ban remains unsettled. State legislatures, in response to the recent court holdings, are reassessing their statutory law regarding NCAs. The *Ryan* Court's holding prevented the FTC's rule from going into effect on September 4, 2024. The Texas and Florida court decisions are awaiting 5th and 11th Circuit Court of Appeals review, respectively. Assuming affirmation of either of the cases on appeal, a circuit split regarding the NCA ban may occur. The US Supreme Court may be called upon to determine the validity of the FTC rule banning NCAs. The Circuit Court decisions are likely to occur in 2025, and any Supreme Court decision would not likely occur until 2026. Meanwhile, state statutory law and common law still apply to NCAs, and the FTC may challenge the validity of NCAs on a case-by-case basis.

US antitrust law remains a potential remedy to scrutinize and restrain inappropriate business practices, including NCA-related abuses. The Sherman Act allows federal and state actors and private citizens to sue for redress. Antitrust cases are typically considered using the "rule of reason" formulated by the Supreme Court in 1911, which requires plaintiffs show that defendant businesses possessing market power did in fact undertake anticompetitive conduct that had or likely had anticompetitive effects. In other words, the court in an antitrust case will require that the plaintiff show that the business actually had a significant controlling market presence in the geographic

Continued on following page

Not All Plant-Based Diets Are Created Equal

BY BECKY MCCALL, MSC, MSCPH

FROM ECCO 2025

BERLIN — Adherence to a healthy plant-based diet is associated with a reduced risk of developing inflammatory bowel disease (IBD), whereas an unhealthy plant-based diet is linked to an increased disease risk and worse outcomes, according to the results of a large cohort study.

The study, which included both Crohn's disease (CD) and ulcerative colitis (UC), also showed that diet quality may affect disease progression and surgery risk for individuals already diagnosed with IBD.

"Not all plant-based foods are equal — they don't all have the same effect on health outcomes," said study researcher, Judith Wellens, MD, PhD, gastroenterology resident at Leuven University Hospital in Belgium.

"We need to look at what people are eating more carefully because it isn't black and white, with all plant-based food being good and animal-based food being bad," said Wellens, who presented the data at the European Crohn's and Colitis Organisation (ECCO) 2025 Congress.

Although she advocates for plant-based diets, Wellens stressed that "they need to be individualized to ensure the overall dietary quality is good. Just cutting out meat products is not very helpful. We think it is the unhealthy additions to some plant-based diets that drive the IBD risk."

Is It the Plants or the Processed Ingredients?

"Preclinical studies have already taught us that plant-based diets alter the gut microbiota in a beneficial way. However, many diets promoted for IBD — for example the Crohn's disease exclusion diet — contain ingredients that are animal based. This is confusing for patients and for clinicians," said Wellens.

To look more closely at the question, she and her colleagues analyzed data for 187,888 participants from the UK Biobank and 341,539 participants from across eight European countries from the European Prospective Investigation Into Cancer and Nutrition (EPIC) cohort. None of the participants had IBD at baseline.

Based on participant 24-hour dietary recalls, the researchers constructed plant-based diet indices (PDIs) with diets categorized as healthy (eg, whole grains, fruits, vegetables, legumes, and vegetarian protein alternatives) or unhealthy (eg, emulsifiers, refined grains, fries, fruit juices, sweets, desserts, sugar-sweetened beverages, and processed foods).

The primary outcome was the incidence of IBD (either CD or UC), whereas the secondary outcome was IBD-related surgery, thereby marking disease progression. Cox regression analysis estimated IBD risk and progression. Incidences of IBD were similar between the two cohorts.

In the UK Biobank cohort, 925 participants developed IBD over a median follow-up of 11.6 years. Participants who followed a healthy PDI had a 25% reduced IBD risk, whereas those who followed an unhealthy PDI had a 48% increased risk for disease development. Both CD and UC showed similar outcomes.

zi3000/iStock/Getty Images

The EPIC cohort had a longer median follow-up time of 14.5 years, during which 548 people developed IBD. Healthy PDIs were linked to a 29% reduced risk for IBD, whereas unhealthy PDIs were associated with a 54% increased risk.

A healthy PDI halved the risk for surgery in participants from the UK Biobank, whereas an unhealthy PDI was associated with a twofold higher risk for surgery.

There were no significant associations between PDIs and other outcomes, such as cardiovascular disease, diabetes, or all-cause mortality.

The researchers also looked at the interactions between genetics and plant-based diets, but those results were not presented at the meeting.

However, Wellens said in an interview that people with a moderate to high risk for IBD based on their polygenetic risk score showed increased odds for IBD risk.

"We don't test people for their genetic risk of IBD, but if people have close relatives with IBD, then there is probably an increased genetic risk of its development," she added.

Commenting on the findings, James Lindsay, PhD, professor of inflammatory bowel disease, Queen Mary University of London, said that several recent epidemiological studies have highlighted "the negative impact of ultra-processed foods on increasing the risk of developing Crohn's disease."

Based on these studies, "one might assume that plant-based diets would be protective," he said, however, the current study shows us "that plant-based diets are not all equal and there are unhealthy aspects to some."

"Of course, showing that a diet is associated with an outcome is not the same as knowing that changing a diet will reduce the risk," Lindsay added. "That requires a well-designed, carefully controlled trial."

Wellens and Lindsay reported no relevant financial disclosures. ■

Continued from previous page

area; and further, that the plaintiff show that the business' actions in fact had an anticompetitive effect, or likely had one. The latter can be found by showing an anticompetitive effect such as abusive pricing.

The FTC's ruling is legally and academically controversial and in fact may not withstand court scrutiny. The rule was put forth by the FTC as an ambitious rule to reduce healthcare spending. But businesses survive only if their revenue surpasses their costs, including personnel costs. Further, maximization of capitalization is attained when businesses require NCAs. Businesses invest heavily in recruiting, hiring, and training personnel, and increased personnel turnover increases these expenditures. NCAs arguably provide a collective benefit by ensuring force continuity, mitigating the risk of the loss of highly trained personnel with proprietary knowledge. NCAs also help a business maintain a skilled workforce, helping maximize business valuation. If FTC's NCA ban rule were ultimately upheld, businesses would likely respond by instituting longer-term employee contracts, extended termination notice periods, and disincentives for employees who do not fully serve their contract length, including substantial financial disincentives. Business valuation might decrease, reducing investment incentives.

NCAs have long been a method of balancing the interests of employees and employers. They protect businesses' confidential information, trade secrets, and patient lists, at some cost to employees pursuing new opportunities. The employee, though, is also provided with some benefit from the NCA, albeit indirect. State statutory law and courts have traditionally worked to ensure an appropriate delicate balance between interests, with courts generally finding unbalanced NCAs unenforceable.

For now, physicians should understand the policy considerations of and recognize the uncertainty surrounding NCAs, become familiar with their state's statutory NCA law, review employment contracts carefully for NCA reasonableness, and seek legal advice if necessary.

Perhaps the FTC's approach is the correct one for our future. Or perhaps the appropriate future of NCA interpretation and enforcement should continue to rest on state statutory law and common law, where antitrust enforcement is on a case-by-case basis, rather than FTC rulemaking. The results of high court decisions, state statutory law changes in response to the FTC rule, and perhaps US congressional action will provide the final answer. ■

Dr. Allen is based at the University of Oklahoma Health Sciences Center in Oklahoma City. He has declared no conflicts of interest in relation to this article.

Safety Profile of GLP-1s Reassuring in Upper Endoscopy

BY WILL PASS
MDedge News

FROM CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

iStock/Getty Images

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are associated with retained gastric contents and aborted procedures among patients undergoing upper endoscopy, according to a meta-analysis of more than 80,000 patients.

Safety profiles, however, were comparable across groups, suggesting that prolonged fasting may be a sufficient management strategy, instead of withholding GLP-1RAs, lead author Antonio Facciorusso, MD, PhD, of the University of Foggia, Italy, and colleagues reported.

"The impact of GLP-1RAs on slowing gastric motility has raised concerns in patients undergoing endoscopic procedures, particularly upper endoscopies," the investigators wrote in *Clinical Gastroenterology and Hepatology* (2024 Aug. doi: 10.1016/j.cgh.2024.07.021). "This is due to the perceived risk of aspiration of retained gastric contents in sedated patients and the decreased visibility of the gastric mucosa, which can reduce the diagnostic yield of the examination."

The American Society of Anesthesiologists recommends withholding GLP-1RAs before procedures or surgery, whereas American Gastroenterological Association (AGA) suggests an individualized approach, citing limited supporting data.

A previous meta-analysis (Am J Gastroenterol. 2024 Jun. doi: 10.14309/ajg.0000000000002820) reported that GLP-1RAs mildly delayed gastric emptying, but clinical relevance remained unclear.

The present meta-analysis aimed to clarify this uncertainty by analyzing 13 retrospective studies that involved 84,065 patients undergoing upper endoscopy. Outcomes were compared among GLP-1RA users vs non-users, including rates of retained gastric contents, aborted procedures, and adverse events.

Patients on GLP-1RAs had significantly higher rates of retained gastric contents than non-users (odds ratio [OR], 5.56), a finding that held steady (OR, 4.20) after adjusting for age, sex, diabetes, body mass index, and other therapies.

GLP-1RAs were also associated with an increased likelihood of aborted procedures (OR, 5.13; 1% vs 0.3%) and a higher need for repeat endoscopies (OR, 2.19; 1% vs 2%); however, Facciorusso and colleagues noted that these events, in absolute terms, were relatively uncommon.

"The rate of aborted and repeat procedures in the included studies was low," the investigators wrote. "This meant that only for every 110 patients undergoing upper endoscopy while in GLP-1RA therapy would we observe an aborted procedure and only for every 120 patients would we need to repeat the procedure."

The overall safety profile of GLP-1RAs in the context of upper endoscopy remained largely reassuring, they added. Specifically, rates of bronchial aspiration were not significantly different between users and non-users. What's more, no single study reported a statistically significant increase in major complications, including pulmonary adverse events, among GLP-1RA users.

According to Facciorusso and colleagues, these findings suggest that retained gastric contents do not appear to substantially heighten the risk of serious harm, though further prospective studies are needed.

'Only for every 110 patients undergoing upper endoscopy while in GLP-1RA therapy would we observe an aborted procedure and only for every 120 patients would we need to repeat the procedure.'

"Our comprehensive analysis indicates that, while the use of GLP-1RA results in higher rates of [retained gastric contents], the actual clinical impact appears to be limited," they wrote. "Therefore, there is no strong evidence to support the routine discontinuation of the drug before upper endoscopy procedures."

Instead, they supported the AGA task force's recommendation for an individualized approach, and not withholding GLP-1RAs unnecessarily, calling this "the best compromise."

"Prolonging the duration of fasting for solids could represent the optimal approach in these patients, although this strategy requires further evaluation," the investigators concluded.

The investigators disclosed no conflicts of interest. ■

Circulating Proteins Predict Crohn's Disease Years in Advance

BY WILL PASS
MDedge News

FROM GASTROENTEROLOGY

Circulating blood proteins could enable early identification of Crohn's disease (CD) years before clinical signs, according to investigators.

The 29-protein biosignature, which was validated across multiple independent cohorts, could potentially open doors to new preclinical interventions, lead author Olle Grännö, MD, of Örebro University in Sweden, and colleagues reported.

"Predictive biomarkers of future clinical onset of active inflammatory bowel disease could detect the disease during 'a window of opportunity' when the immune dysregulation is potentially reversible," the investigators wrote in *Gastroenterology* (2024 Nov. doi: 10.1053/j.gastro.2024.11.006).

Preclinical biomarker screening has proven effective in other immune-mediated diseases, such as type 1 diabetes, where risk stratification using autoantibodies enabled early intervention that delayed disease onset, they noted.

Previous studies suggested similar potential for inflammatory bowel disease (IBD) via predictive autoantibodies and serum proteins, although the accuracy of these markers was not validated in external cohorts. The present study aimed to fill this validation gap.

First, the investigators measured 178 plasma proteins in blood samples taken from 312 individuals before they were diagnosed with IBD. Using machine learning, Dr. Grännö and colleagues compared these findings with blood-matched controls who remained free of IBD through follow-up. This process revealed the 29-protein signature.

In the same discovery cohort, the panel of 29 proteins differentiated preclinical CD cases from controls with an area under the curve (AUC) of 0.85. The signature was then validated in an independent preclinical cohort of CD patients, with an AUC of 0.87.

While accuracy increased in proximity to clinical disease onset, the model was still highly predictive up to 16 years before CD diagnosis, at which time the AUC was 0.82. The panel showed perfect performance among newly diagnosed CD patients, with an AUC of 1.0, supporting clinical relevance.

Predictive power was statistically significant but less compelling among individuals with preclinical ulcerative colitis (UC). In this IBD subgroup, AUC for identification and validation cohorts was 0.77 and 0.67, respectively, while newly diagnosed patients had an AUC of 0.95.

"In preclinical samples, downregulated (but not upregulated) proteins related to gut barrier integrity and macrophage functionality correlated with time to diagnosis of CD," Dr. Grännö and colleagues wrote. "Contrarily, all proteins associated with preclinical UC were upregulated, and only one protein marker correlated with the time to diagnosis."

These findings suggest that disruptions in gut barrier integrity and macrophage function precede clinical CD onset, they explained, potentially serving as an early signal of inflammation-driven intestinal damage. In contrast, the preclinical UC signature primarily involved upregulated inflammatory markers.

Dr. Grännö and colleagues also examined the influence of genetic and environmental factors by comparing preclinical IBD signatures in unrelated and related twin pairs.

The CD biosignature had an AUC of 0.89 when comparing individuals with preclinical CD to matched external (unrelated) healthy twins. Predictive ability dropped significantly (AUC = 0.58) when comparing CD cases to their own healthy twin siblings, suggesting that genetic and shared environmental factors have a "predominant influence" on protein dysregulation.

In contrast, AUC among unrelated vs related twin controls was more similar for UC, at 0.76 and 0.64, respectively, indicating "a limited impact" of genetic and environmental factors on the protein signature.

Ultimately, the study highlights the potential for early detection and intervention, the authors said.

"The long preclinical period in CD endorses the adoption of early preventive strategies (eg, diet alterations and medication) to potentially attenuate disease progression and improve the natural history of CD," they concluded.

This study was funded by the Swedish Research Council and other organizations. The investigators disclosed relationships with Pfizer, Janssen, AbbVie, and others. ■

Nowadays, preclinical biomarker discovery for inflammatory bowel diseases (IBD) is one of the key areas of study, aiming to identify the earliest stages of disease development and to find opportunities for early intervention. The study by Grännö and colleagues taps into this area and provides a significant advancement in the early detection of Crohn's disease (CD) with a validated 29-plasma protein biomarker signature.

With an area under the curve of up to 0.87 in preclinical CD cases and even 0.82 as early as 16 years before diagnosis, these findings strongly support the notion that CD has a prolonged preclinical phase that is detectable up to many years before diagnosis. Importantly, their identified protein signatures also shed light on distinct pathophysiological mechanisms between CD and ulcerative colitis (UC), with CD characterized by early disruptions in gut barrier integrity and macrophage function, while UC was more marked by upregulated inflammatory markers.

For clinical practitioners, these findings have a strong transformative potential. Following further validation in larger cohorts and allowing clinical accessibility, preclinical biomarker screening could become a routine tool for risk stratification in at-risk individuals, such as those with a strong family history or genetic predisposition. This could enable implementation of early interventions, including dietary modifications and potentially prophylactic therapies, to delay or even prevent disease onset. Given that similar approaches have proven effective in type 1 diabetes, applying this strategy to IBD could significantly alter disease progression and patient outcomes.


Dr. Bourgonje

Challenges remain before implementation in clinical practice could be realized. Standardized thresholds for risk assessment, cost-effectiveness analyses, and potential therapeutic strategies tailored to biomarker-positive individuals require further exploration. However, this study provides important data needed for a paradigm shift in IBD management — one that moves from reactive treatment to proactive prevention.

Arno R. Bourgonje, MD, PhD, is a postdoctoral fellow at the division of gastroenterology, Icahn School of Medicine at Mount Sinai, New York, and at the University Medical Center Groningen in the Netherlands. He is involved in the European INTERCEPT consortium, which is focused on prediction and prevention of IBD. He reported no conflicts of interest.


COURTESY HÅKAN RISBERG, REGION ÖREBRO LÄN

Dr. Olle Grännö (left) and Dr. Jonas Halfvarson are, respectively, the lead and principal authors of a study demonstrating how circulating blood proteins could enable early identification of Crohn's disease.

Updated Guidance From AGA

Reactivation *from page 1*

patient-, drug-, and disease-specific factors — and so it can range from very rare to more frequent," said guideline coauthor Tracey G. Simon, MD, MPH, a hepatologist in the division of gastroenterology at Massachusetts General Hospital and an instructor at Harvard Medical School, both in Boston. "Not every at-risk individual needs pharmacologic treatment, but some certainly do, and this guideline was designed to try to better identify who needs treatment, based on those important drug- and virus-specific factors."

Dr. Simon

'Not every at-risk individual needs pharmacologic treatment, but some certainly do, and this guideline was designed to try to better identify who needs treatment, based on ... drug- and virus-specific factors.'

Simon stressed the importance of creating this guideline to include many new therapies that carry varying degrees of reactivation risk. As to the strength of the evidence, she added, "for some of the questions, the panel was satisfied with the level of certainty. However, for other questions, the data are still very sparse, and so we have tried to ensure that these areas of uncertainty are highlighted clearly for providers and patients."

Main Recommendations

AGA based its clinical recommendations on balancing desirable and undesirable effects, patient values and preferences, costs, and health equity considerations. It also provided a clinical decision support tool for making pharmacologic management decisions.

The panelists reviewed data on multiple immunosuppressive therapies from older agents such as anthracycline derivatives, corticosteroids, and anti–tumor necrosis factor (anti-TNF) drugs to chimeric antigen receptor T cells and recent biologics and inhibitors.

1. For individuals at high risk for HBVr, AGA recommended antiviral prophylaxis over monitoring alone. Strong recommendation, moderate-certainty evidence.
Implementation considerations: Use antivirals with a high barrier to resistance. Prophylaxis should be started before initiating medications that carry a risk for HBVr and should be continued for at least 6 months after discontinuation of risk-imposing therapy (at least 12 months for B cell–depleting agents).

2. For individuals at moderate risk for HBVr, antiviral prophylaxis was recommended over monitoring alone. Conditional recommendation, moderate-certainty evidence.
Implementation considerations: Use antivirals with a high barrier to resistance. Patients who place a higher value on avoiding long-term antiviral therapy and its associated cost and place a lower value on avoiding the small risk of reactivation (particularly those who are hepatitis B surface antigen [HBsAg]–negative) may reasonably select active monitoring over antiviral prophylaxis.

Careful consideration should be given to the feasibility and likelihood of adherence to long-term monitoring performed at 1- to 3-month intervals and including assessment of hepatitis B viral load and alanine aminotransferase.

3. For low-risk individuals, the AGA said monitoring alone may be used. Conditional recommendation, moderate-certainty evidence.
Implementation considerations: This recommendation assumes regular and sufficient follow-up with continued monitoring. Patients who place a higher value on avoiding the small risk of reactivation (particularly those on more than one low-risk immunosuppressive) and a lower value on the burden and cost of antiviral therapy may reasonably select antiviral therapy.

4. For individuals at risk for HBVr, the guideline recommended testing for hepatitis B. Strong recommendation, moderate-certainty evidence.
Implementation considerations: Given the Centers for Disease Control and Prevention's universal screening guidance on hepatitis B for everyone aged 18 years or older by testing for HBsAg, anti-HBs, and total anti–hepatitis B core (HBc), the guideline said that stratifying screening practices by magnitude of HBVr risk is no longer needed.

It is reasonable to test initially for serologic markers alone (at minimum for HBsAg or anti-HBc) followed by viral load testing (HBV-DNA) if HBsAg and/or anti-HBc is positive.

Hepatitis C Virus (HCV) Coinfection With Direct-Acting Antiviral (DAA) Treatment

The panel identified 11 studies that provided data for the computation of baseline risk for HBVr in the HCV coinfection cohort undergoing DAA therapy.

In patients who were HBsAg-positive, the pooled baseline risk for HBVr was 240 per 1000, categorizing them to be at high risk for HBVr. The panel stated it is therefore reasonable to extend antiviral prophylaxis beyond the 12-24 weeks of DAA therapy to 6-12 months after cessation of DAA therapy, tailored by clinician judgment and patient preference.

A 'Useful Clinical Tool'

Commenting on the guideline but not involved in it, Saikiran Kilaru, MD, a hepatologist at NYU Langone Health in New York City, said the update is "absolutely a useful clinical tool. Since the prior guidance was published, there has been a deluge of new medications and medication classes. Prior to the guidance, I was making recommendations based on the limited data available for hepatitis B reactivation risk for these new medications, using the 1%-10% moderate-risk category as guidance."

Dr. Kilaru

'The AGA guidance is 'absolutely a useful clinical tool. ... Prior to the guidance, I was making recommendations based on the limited data available for hepatitis B reactivation risk for ... new medications.'

In addition, Kilaru said, this guidance is driven by a higher level of evidence certainty than the mostly retrospective evidence that was previously available.

She cautioned that few downgraded risk categories are likely to cause consternation among physicians who have been operating without the benefit of larger meta-analyses of HBVr in new medication categories. "For example, the prior guidance had put anti-TNF as of moderate risk for hepatitis B core–positive-only patients and is now downgraded to low risk." And other medications such as immune checkpoint inhibitors, which seemed to pose at least moderate risk based on smaller, retrospective studies are now considered to be in the low-risk category.

"It may take some time for these recommendations to be adopted, especially for physicians in the community who have seen fatal or severe reactivations in the past few years," Kilaru said.

Kilaru pointed out that the guidance update does not clearly cover some standard immunosuppressive therapies used in autoimmune, rheumatologic, and posttransplant regimens, such as mycophenolate, tacrolimus, and cyclosporine. Nor does it address HBVr risk in some liver cancer treatments such as yttrium-90, which have been associated with reports of HBV.

The Future

According to Simon, more data are needed to better estimate HBVr risk in several important settings, including treatment with the most recently approved immunosuppressive drugs for which data are still limited, as well as combination treatments.

Kilaru noted that guideline updates such as this become increasingly relevant as cancer diagnoses rise and hepatitis B exposure and detection increase as well.

The AGA panel acknowledged that uncertainty remains in some patient risk categorizations. "As the armamentarium of immunotherapeutics evolves, it will be crucial to search for, use, and maintain studies that provide baseline HBV serologies; include a clear definition of HBVr; and enroll a large, nonselective cohort that can guide categorization of risk of HBVr," the panelists wrote.

AGA provided all financial support for the development of this guideline. No funding from industry was offered or accepted to support the writing effort.

The authors reported no relevant competing interests, but one coauthor is an adviser for Gilead Sciences, and other authors disclosed various relationships with multiple private sector companies. Kilaru had no competing interests to disclose. ■

New Model Estimates Hepatocellular Carcinoma Risk in Patients With Chronic Hepatitis B

BY CAROLYN CRIST

A new prognostic model could potentially predict and stratify the risk for hepatocellular carcinoma (HCC) among patients with chronic hepatitis B (CHB) who are noncirrhotic and not indicated for antiviral treatment.

The model, called Revised REACH-B or reREACH-B, stems from cohort studies in Hong Kong, South Korea, and Taiwan, and looks at the nonlinear parabolic association between serum hepatitis B virus (HBV) DNA levels and HCC risk.

"Current clinical practice guidelines don't advocate antiviral treatment for patients with CHB who don't show elevated alanine aminotransferase (ALT) levels, even in those with high HBV viral loads," said coauthor Young-Suk Lim, MD, PhD, professor of gastroenterology at the University of Ulsan College of Medicine and Asan Medical Center in Seoul, South Korea.

"This stance is rooted in the notion that patients in the immune-tolerant phase are at very low risk for developing HCC," Lim said. "However, the immune-tolerant phase includes patients with HBV DNA levels who face the highest risk for HCC, and many patients with moderate HBV viremia fall into an undefined gray zone."

The study was published in *Annals of Internal Medicine* (2024 Sep. doi: 10.7326/M24-0384).

Validating reREACH-B

During a course of CHB, HBV viral loads and HCC risks evolve over time because of viral replication and host immune responses, Lim explained. Most patients typically move to seroclearance and an "inactive hepatitis" phase, but about 10%-20% can progress to a "reactivation" phase, where HBV DNA levels and ALT levels increase, which can increase HCC risk as well.

In a previous cohort study in Taiwan, a prognostic model called Risk Estimation for HCC in CHB — or REACH-B — found the risk for HCC increases 10-fold with increasing levels of HBV DNA up to 5 $\log_{10}$IU/mL in noncirrhotic patients with CHB, regardless of ALT levels. Another cohort study in South Korea found a nonlinear parabolic association between HCC risk and HBV DNA levels up to 9 $\log_{10}$ IU/mL, with the highest risks found for moderate HBV DNA levels around 6 $\log_{10}$ IU/mL.

'In contrast to most chronic liver diseases where liver cancer develops only among those with advanced fibrosis/cirrhosis, people with chronic hepatitis B are at risk prior to the development of cirrhosis.'

In this study, Lim and colleagues developed a prognostic model to integrate the nonlinear relationship and validated it externally, as well as compared it with the previous REACH-B model. The Revised REACH-B model incorporates six variables: age, sex, platelet count, HBV DNA level, ALT, and hepatitis B e-antigen (HBeAg).

The study included 14,378 treatment-naive, noncirrhotic adults with CHB and serum ALT levels less than two times the upper limit of normal for at least 1 year and serum hepatitis B surface antigen for at least 6 months. The internal validation cohort included 6949 patients from Asan Medical Center, and the external validation cohort included 7429 patients from previous studies in Hong Kong, South Korea, and Taiwan.

Among the Asan cohort, the mean age was 45 years, 29.9% were HBeAg-positive, median HBV DNA levels were 3.1 $\log_{10}$ IU/mL, and the median ALT level was 25 U/L. In the external cohort, the mean age was 46 years, 21% were

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Member SPOTLIGHT

Childhood IBD Connects PA With Her Patients

BY JENNIFER LUBELL
MDedge News

Abigail Meyers, MPAS, PA-C, was 9 years old when a diagnosis of ulcerative colitis set the trajectory of her future career.

"There weren't a lot of medical therapies available back then," recalls Meyers, who had to undergo multiple hospitalizations and surgeries for her condition. Medical staff would say: "Oh I know how you feel," then retract their words when Meyers would ask if they had ever experienced a nasogastric tube or ileostomy.

"I'm going to go into healthcare. I'm going to take care of patients with inflammatory bowel disease [IBD] and I will never say 'I know how you feel' unless I truly mean it," Meyers vowed to her mother one night at the hospital.

And that's exactly what she did. During her training as a physician assistant (PA), Meyers had the opportunity to do an adult colorectal surgery rotation and a pediatric gastroenterology rotation. Another bonus: She got to work with the gastroenterologist who treated her when she was a 9-year-old patient.

Meyers has never told a patient,

COURTESY ABIGAIL MEYERS

Abigail Meyers was 9 years old when a diagnosis of ulcerative colitis set the trajectory of her future career.

"I know how you feel." Instead, she might say: "This is really hard. This is something new. This is a challenging moment. You're allowed to feel upset, you're allowed to feel disappointed, you're allowed to feel scared."

A clinical expert in gastroenterology and colon and rectal surgery, Meyers spent 10 years at the Mayo Clinic as a PA in colon and rectal surgery and gastroenterology. She currently works as the assistant director of student success and development at the Medical College of Wisconsin in Milwaukee.

On days where things are hard and the grind of the day-to-day work in healthcare becomes too challenging, "I get to remind myself that I do make an impact," said Meyers. If a patient ever asks her, "Have you ever had an ileostomy before?" Meyers can honestly answer that she has and then describe what it was like.

"I think that allows them to have a little bit of an 'aha' moment or a breakthrough in their recovery journey or their acceptance journey, whatever that looks like through this disease process," she said.

In an interview, she discussed the work she's done on multiple fronts to guide the careers of advanced practice providers (APPs), and the special connection she has with her patients.

Tell me about your preceptor work with the Crohn's and Colitis Foundation's APP Preceptorship program.

It is one of my proudest accomplishments, particularly in the preceptorship program. As a patient, the Crohn's and Colitis Foundation provided a lot of education and resources when my family was going through a tough time. To be able to give back to the foundation, whether that's resources for patients or providers, is really great. It's helped me grow a lot professionally. I realized I enjoyed educating not just my patients, but also my peers. While I worked at Mayo Clinic, I had a wonderful opportunity at a tertiary IBD center for students and advanced practice providers to come and shadow me in colorectal surgery and managing IBD patients.

'As we seek to develop academically minded physician associates to join academic medical practices in an anticipated physician shortage, we want to hone in on some of these specialty care areas.'

Michele Rubin, MSN, an advanced practice nurse and Maureen Kelly, MS, RN, CPNP, a nurse practitioner, started the foundation's preceptor program and graciously took me under their wing.

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HBeAg-positive, median HBV DNA levels were 3.4 $\log_{10}$ IU/mL, and the median ALT level was 20 U/L.

In the Asan cohort, 435 patients (6.3%) developed HCC during a median follow-up of 10 years. The annual HCC incidence rate was 0.63 per 100 person-years, and the estimated cumulative probability of developing HCC at 10 years was 6.4%.

The association between HBV viral load and HCC risk was linear in the HBeAg-negative groups and inverse in the HBeAg-positive groups, with the association between HBV viral load and HCC risk showing a nonlinear parabolic pattern.

In the external cohort, 467 patients (6.3%) developed HCC during a median follow-up of 12 years. The annual HCC incidence rate was 0.42 per 100 person-years, and the estimated cumulative probability of developing HCC at 10 years was 3.1%.

Overall, the association between HBV viral load and HCC risk was linear in the HBeAg-negative groups and inverse in the HBeAg-positive groups, with the association between HBV viral load and HCC risk showing a nonlinear parabolic pattern.

Across both cohorts, patients with HBV DNA levels between 5 and 6 $\log_{10}$ IU/mL had the highest risk for HCC in both the HBeAg-negative and HBeAg-positive groups, which was more than eight times higher than those with HBV DNA levels ≤ 3 $\log_{10}$ IU/mL.

For internal validation, the Revised REACH-B model had a c-statistic of 0.844 and 5-year area under the curve of 0.864. For external validation across the three external cohorts, the reREACH-B had c-statistics of 0.804, 0.808, and 0.813, and 5-year area under the curve of 0.839, 0.860, and 0.865.

In addition, the revised model yielded a greater positive net benefit than the REACH-B model in the threshold probability range between 0% and 18%.

"These analyses indicate the re-REACH-B model can be a valuable tool in clinical practice, aiding in timely management decisions," Lim said.

Considering Prognostic Models

This study highlights the importance of recognizing that the association between HBV DNA viral load and HCC risk isn't linear, said Norah Terrault, MD, chief of gastroenterology and hepatology at the Keck School of Medicine at the University of Southern California, Los Angeles.

"In contrast to most chronic liver diseases where liver cancer develops only among those with advanced fibrosis/cirrhosis, people with chronic hepatitis B are at risk prior to the development of cirrhosis," she said. "Risk prediction scores for HCC can be a useful means of identifying those without cirrhosis who should be enrolled in HCC surveillance programs."

For instance, patients with HBV DNA levels < 3 $\log_{10}$ IU/mL or > 8 $\log_{10}$ IU/mL don't have an increased risk, Terrault noted. However, the highest-risk group appears to be around 5-6 $\log_{10}$ IU/mL.

"Future risk prediction models should acknowledge that relationship in modeling HCC risk," she said. "The re-REACH-B provides modest improvement over the REACH-B, but further validation of this score in more diverse cohorts is essential."

The study received financial support from the Korean government and grants from the Patient-Centered Clinical Research Coordinating Center of the National Evidence-Based Healthcare Collaborating Agency and the National R&D Program for Cancer Control through the National Cancer Center, which is funded by Korea's Ministry of Health and Welfare. Lim and Terrault reported no relevant disclosures. ■

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Originally, there was just one site at the University of Chicago. When I joined, it expanded to the University of North Carolina at Chapel Hill for pediatric experience, and Mayo Clinic Rochester [Minnesota]. There are now seven participating host sites for the 2025 cycle.

The curriculum varies at each site based upon what resources are available. We really tried to tailor it to each individual preceptor. If there's a nurse practitioner that used to be an ostomy nurse, maybe she'll get time in the ostomy nurse area, but maybe she wants more time with the pharmacist or the radiologist.

If there is somebody who's coming through the program who knows nothing about surgery, maybe they want a little bit more time in the surgical sphere. I tried to, when creating the curriculum for this, create a lot of options that existed for didactic learning as well as practical application.

Lightning Round

Dream profession if you weren't a GI?
First grade teacher

Last movie you watched?
Mufasa: The Lion King

Best Halloween costume?
Velma from Scooby Doo

Favorite sport?
To play – Tennis
To watch – NBA basketball, "Go Timberwolves!"

Place you most want to travel to?
Greece

Favorite movie genre?
Rom-com

Cat person or dog person?
Cat

Favorite city besides the one you live in?
Manhattan

Favorite season?
Fall

Favorite junk food?
Salty snack mix

Number of cups of coffee you drink per day?
Three

You're the assistant director of student success and development at the Medical College of Wisconsin, which launched a new Physician Associate Program. What's happened with the program so far?
We do not have enrolled students yet. We are developing the program from the bottom up. I am one of four faculty, and then we have our founding director, Christine M. Everett, PhD, MPH, PA-C.

'We are trying to create a sense of community within all the societies that APPs are involved in, and recognize everyone's professional development and goals. We want to create a space to connect at some of our primary conferences.'

As we develop our program we are trying to keep a holistic approach in mind. We're thinking about what a traditional student is vs a nontraditional student, and who we think will make great physician assistants. We pull from our own personal experiences as educators and experts in our field. As somebody who is academically minded, this program really spoke to me. Many PAs and nurse practitioners (NPs) fill a primary care role. But as we seek to develop academically minded physician associates to join academic medical practices in an anticipated physician shortage, we want to hone in on some of these specialty care areas, recognizing that there is a place for us in academia and asking "what does that look like and how do we grow in those subspecialties?"

I have always wanted to work in GI [gastrointestinal] or colorectal surgery. Subspecialty wise, I really like the IBD disease process. So, how can I help to foster that type of desire and growth and professional development in my students? That will be what we're going to be tackling in our future cohorts.

Has the program generated a lot of interest?
Most PAs train in the region they are from and end up practicing there. So, our community and institution are very excited. There's a lot of work in creating the program and making sure that the goals we have in mind will continue to grow with the profession. One of my neighbors who just started college reached out to me and said she wants to be a PA. We get emails regularly asking what people should do to prepare for PA school, and what are we looking for. PAs and NPs are growing professions. Both are on the top five list of best jobs ranked by *U.S. News & World Report* right now.

You're the co-chair of AGA's NPPA Task Force. What are the goals of this task force, specifically for 2025?
This is a new task force. We're really excited about it, and we feel very supported by AGA [American Gastroenterological Association]. Specifically, we are focusing on content review and optimization. We're working through and consulting on different proposals, such as how to have an NP/PA voice within AGA, or how certain proposals can be of interest to APPs or applicable to an APP practice.

One of our other goals is to grow our APP community opportunities, to find ways that we can all communicate with each other, share in our professional accomplishments, and be mentors and sponsors to each other to open the doors for professional growth within the GI space.

We are trying to create a sense of community within all the societies that APPs are involved in, and recognize everyone's professional development and goals. We want to create a space to connect at some of our primary conferences and touchpoints, regardless of where your society home is.

We've also been asked to be a representative in helping to select the AGA-Pfizer Beacon of Hope Awards for Gender and Health Equity award recipients. We're really proud that one of our task force members is going to be sitting on that committee to help select recipients of this award.

As a clinical expert in gastroenterology and colon and rectal surgery, you often present to national organizations like AGA, the Crohn's and Colitis Foundation, and the American Society of Colon & Rectal Surgeons. What topics do you discuss and why?
It's always been IBD because of my background. But I've also grown more in the colon/rectal surgery sphere, both in the inpatient, outpatient, and operating room setting. I enjoy presenting on topics like: What could you do right before you send a patient off to a tertiary IBD referral? I talk about complex disease management, especially the surgical realm of perianal Crohn's disease. One of my colleagues jokes that one of her favorite talks I've ever given is how to perform a perianal examination. It's a sensitive exam. I feel like I'm pretty good at it!

I also think it's important to share information on how to write papers and how to present at conferences, because there are a lot of really smart NPs and PAs in GI and colorectal surgery who — for whatever reason — don't know how to get their foot in the door for these types of opportunities. I love to be the person that opens that door. Do you want to be involved in a professional society? In what capacity? Making that information broadly available to everyone is something that I really love doing.

Describe a memorable patient encounter that helped shape your career.
I know this will sound so cliché, that there isn't just one, but it's true. There is a connection that I create with each and every one of my patients. I listen to their stories. They have whole lives outside of their disease, and I am honored that they open up to me — whether that is ongoing communication and check-ins with a patient's family member a year after they've passed away, or every year receiving a Christmas card from a patient who is expanding their family because they're finally in remission from their disease. These are the types of things that are so impactful and memorable.

'There is a connection that I create with each and every one of my patients. I listen to their stories. They have whole lives outside of their disease, and I am honored that they open up to me.'

Describe how you would spend a free Saturday afternoon.
I'm a mom to 7-year-old boy twins, and so I often don't have a free Saturday. If I did, it would be sunny. I would go for a long run and then I would go out for brunch with my husband and then come home and read with my kids in a cozy blanket all day. ■

Molecular Stool Testing Could Cut Post-Polypectomy Colonoscopies by 15%-41%

BY DIANA SWIFT

FROM GASTROENTEROLOGY

Noninvasive surveillance with multitarget stool DNA testing or fecal immunochemical testing (FIT) could potentially match colonoscopy for reducing long-term colorectal cancer (CRC) incidence and mortality. It might also reduce colonoscopies by an estimated 15%-41%.

The greatest reduction would likely be achieved by annual FIT-based surveillance, especially with FIT FOB-Gold at a threshold of at least 32 µg/g feces, according to findings from the Dutch MOCCAS study published in *Gastroenterology* (2024 Aug. doi: 10.1053/j.gastro.2024.08.022).

In this cross-sectional observational study, the multitarget DNA test outperformed FIT for detecting advanced precursor lesions, especially serrated polyps. According to long-term-impact mathematical modeling, however, DNA-based surveillance would be more costly than colonoscopy surveillance, whereas FIT would save costs.

"With the worldwide implementation of FIT-based screening programs, following a positive test, many more people enter surveillance programs after polypectomy. This results in an increased pressure on the colonoscopy capacity and healthcare budgets," lead author Beatriz Carvalho, PhD, a molecular biologist in the department of pathology of the Netherlands Cancer Institute in Amsterdam, said in an interview.

Dr. Carvalho

A noninvasive strategy could ease the surveillance burden on healthcare resources and be more palatable to patients. Post-polypectomy guidelines have already been relaxed to allow less intensive surveillance.

"Our working hypothesis was that although the sensitivity of a singular molecular test to detect CRC or advanced adenomas is lower than that of colonoscopy, repeating molecular stool testing would yield similar detection rates as colonoscopy-based surveillance. And our hypothesis was confirmed," Carvalho said.

The results of the MOCCAS study align with those of other studies that found that FIT could be safely applied as a triage test in post-polypectomy surveillance and could safely extend the interval of surveillance colonoscopy. "But these studies did not include a long-term impact analysis," she said. "The next step is to run a prospective interventional study to validate the MOCCAS findings."

Offering an outsider's perspective on the findings, Uri Ladabaum, MD, director of the Gastrointestinal Cancer Prevention Program and a professor of medicine at Stanford University School of Medicine in Palo Alto, California, said the real-world results on lesion detection and the multi-year-horizon modeling performed are provocative and point to the potential to base post-polypectomy surveillance on stool tests.

He cautioned, however, that the proposed paradigm requires the ability to deploy FIT-based surveillance with broad flexibility in relation to hemoglobin-detection thresholds and testing interval, depending on the specific FIT that is chosen, with the possibility these may differ by setting based on the characteristics of the population and the relevant epidemiology.

"Such flexibility may or may not be technically feasible in all settings — for instance, in the current US regulatory context, it would be challenging to implement FIT-based testing at newly adjusted detection thresholds," he said.

Nevertheless, the study provides a strong rationale for a real-world study of FIT-based surveillance, he added. "The choice of specific FIT and detection threshold will be critical. Multiple rounds of FIT-based surveillance, that is, years of prospective surveillance, will be needed to constitute a properly designed comparison with surveillance colonoscopy."

Study Details

The cross-sectional observational study included individuals aged 50-75 years who provided stool samples for the DNA test and two FITs. Test accuracy was calculated for all surveillance indications.

For the post-polypectomy indication only, which is the most common and associated with a relatively low CRC risk, the long-term impact of stool-based surveillance was evaluated with the Adenoma and Serrated Pathway to Colorectal Cancer model. Stool-based strategies were simulated to tune each test's positivity threshold to obtain strategies that are at least as effective as colonoscopy surveillance.

A total of 3453 individuals had results for all stool tests and colonoscopy; among them, 2226 had previously undergone polypectomy, 1003 had a history of CRC, and 224 had a familial risk.

Areas under the receiver operating characteristic curve for advanced neoplasia were as follows:

- 0.72 (95% CI, 0.69-0.75) for the multitarget stool DNA test
- 0.61 (95% CI, 0.58-0.64) for the FIT OC-SENSOR
- 0.59 (95% CI, 0.56-0.61) for the FIT FOB-Gold

Stool-based surveillance was estimated to be at least as effective as colonoscopy surveillance and required 5.6-9.5 stool tests over a person's lifetime. DNA-based surveillance was more costly than colonoscopy surveillance, whereas FIT-based surveillance saved costs.

"These findings provide a basis to embark on a prospective intervention study to assess the clinical utility of FIT as an alternative to colonoscopy surveillance in a post-polypectomy CRC surveillance population," the authors wrote.

Continued on following page

Subcutaneous Induction Safety

Guselkumab *from page 1*

showed the efficacy of induction of IV guselkumab and subcutaneous maintenance in patients with UC, the ASTRO study randomly assigned 418 patients with moderately to severely active UC to receive either induction with 400 mg subcutaneous guselkumab at weeks 0, 4, and 8 or placebo.

After induction, the treatment group received a maintenance dose of either 200 mg subcutaneous guselkumab at week 12 and then every 4 weeks or 100 mg every 8 weeks (starting week 16).

All patients had an inadequate response or intolerance to conventional therapy. Around 60% were naive to biologics, Janus kinase (JAK) inhibitors, or sphingosine-1-phosphate receptor modulators (S1Ps).

Clinical remission at week 12 — the primary endpoint — was achieved by 27.6% of all patients treated with guselkumab compared with 6.5% of patients on placebo.

"These results are in line with the QUASAR data," in which clinical remission was 22.6% with IV guselkumab at 12 weeks, noted Peyrin-Biroulet.

Clinical remission was achieved at week 12 by 36% of patients naive to biologics, JAK inhibitors, or S1Ps in the guselkumab group and by 8.9% of these patients in the placebo group ($P < .001$). Among patients who had previously received biologics, JAK inhibitors, or S1Ps, 16.1% of those in the guselkumab group achieved clinical remission compared with 3.6% of those in the placebo group ($P = .005$).

"In terms of symptomatic remission at week 12, the difference between the overall guselkumab result and placebo was 30%," reported Peyrin-Biroulet.

Clinical response — defined as a decrease in the modified Mayo score by ≥ 30% and ≥ 2 points, with either a ≥ 1-point decrease from baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1 — was 65.6% in the guselkumab group compared with 34.5% in the placebo group ($P < .001$).

Among patients naive to biologics, JAK inhibitors, or S1Ps, clinical response was 71.3% in the guselkumab group, compared with 41.8% in the placebo group ($P < .001$). Among those who had previously received biologics, JAK inhibitors, or S1Ps, it was 57.1% in the guselkumab group, compared with 25.0% in the placebo group ($P < .001$).

Turning to endoscopic improvement (ie, an endoscopic subscore of 0 or 1 with no friability), 37.3% of those in the guselkumab group overall, compared with 12.9% of those in the placebo group who achieved this endpoint ($P < .001$).

"This is a treatment effect of over 20%," said Peyrin-Biroulet. "We know that when it is over 20%, it is considered game changer."

In patients naive to biologics, JAK inhibitors, or S1Ps, endoscopic improvement was 45.7% with guselkumab vs 17.7% with placebo. In those who had previously received biologics, JAK inhibitors, or S1Ps, endoscopic improvement was 24.1% with guselkumab vs 7.1% with placebo. Both were statistically significant.

The safety of subcutaneous induction therapy was consistent with the well-characterized and favorable safety profile of guselkumab in approved indications.

The GRAVITI Study

In the phase 3, randomized, double-blind, placebo-controlled GRAVITI study, also presented at ECCO 2025 Congress, researchers evaluated the efficacy and safety of induction with subcutaneous guselkumab followed by subcutaneous maintenance compared with placebo in patients with moderately to severely active Crohn's disease.

The GRAVITI study followed the same induction and maintenance dosage and treatment intervals as the ASTRO study.

In addition, the patients randomly assigned to placebo were able to receive subcutaneous guselkumab (400 mg every 4 weeks followed by 100 mg every 8 weeks) if rescue criteria were met at week 16.

The co-primary endpoints were clinical remission and endoscopic response at week 12.

Ailsa Hart, MD, director, IBD research, St. Mark's Hospital and Imperial College, both in London, reported the 12-week and 48-week results, which were initially presented at the American College of Gastroenterology meeting in October 2024.

Regarding the 48-week results ... the rate of clinical remission was more than three times higher with both maintenance doses of guselkumab at 66.1% (200 mg) and 60.0% (100 mg) vs 17.1% with placebo.

At week 12, 56.1% of patients who received guselkumab achieved clinical remission, compared with 21.4% of patients who received placebo. Endoscopic response was achieved in 41.3% of patients treated with guselkumab compared with 21.4% in the placebo group.

Regarding the 48-week results, Hart noted that the rate of clinical remission was more than three times higher with both maintenance doses of guselkumab at 66.1% (200 mg) and 60.0% (100 mg) vs 17.1% with placebo.

Endoscopic response at 48 weeks was achieved in 51.3% of patients on the 200-mg maintenance dose and in 44.3% on the 100-mg maintenance dose, compared with 6.8% of patients on placebo.

In addition, endoscopic remission was achieved in 38.3% of patients in the 200-mg guselkumab group and in 30.4% in the 100-mg guselkumab group, compared with 6.0% in the placebo group.

Safety findings were consistent with the known safety profile of guselkumab in approved indications and other studies in IBD.

"These results complement the GALAXI data and demonstrate that both IV and subcutaneous guselkumab induction are efficacious and therapeutic in Crohn's disease," Hart said. Furthermore, data from the ASTRO study demonstrated similar data in the UC population.

As clinicians, this gives us flexibility in how we treat our patients; although, the rationale for choosing subcutaneous or IV is likely to be pragmatic, Hart said.

Additionally, the flexibility of the maintenance therapy, that is, 200 mg subcutaneous guselkumab every 4 weeks or 100 mg every 8 weeks, "is expected to positively affect several parameters of therapy, including increased compliance, hospital avoidance, and better safety profiling," comoderator Giorgos Bamias, MD, professor of gastroenterology at the National and Kapodistrian University of Athens, said.

It appears that multiple options will be offered to patients regarding treatment with guselkumab for patients with Crohn's disease, Bamias said. "Interestingly, a similar multiplicity of options has also been shown for ulcerative colitis, through the QUASAR and ASTRO studies."

Peyrin-Biroulet declared receiving grants and other support/travel from multiple companies. Hart declared receiving grants and personal fees from multiple companies. Bamias declared receiving grants and personal fees/honoraria as an adviser/lecturer from multiple companies. ■

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In the United States, Ladabaum said, it would likely be possible to find FIT-based strategies that closely approximate or match surveillance colonoscopy — "if we could deploy FIT with the required flexibility, for example, by adjusting the threshold and if the reference surveillance standard were somewhat relaxed compared with current guidelines."

He worries, however, that if FIT for screening and FIT for surveillance were optimized at different hemoglobin detection thresholds, "there could be confusion and room for error in real-world clinical implementation."

Dr. Ladabaum

The authors called for research to increase understanding of the mechanisms underlying progression from adenomas to malignancy over time, which may yield better biomarkers to improve stool test accuracy.

This study was funded by the Alpe d'HuZes charity and the Dutch Cancer Society. Exact Sciences provided test equipment and performed multitarget stool DNA test analysis. Sentinel Diagnostics provided equipment and reagents.

Carvalho and coauthor Veerle M. H. Coupé, PhD, disclosed several patents pending and/or issued.

Ladabaum disclosed no competing interests relevant to his comments. ■

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