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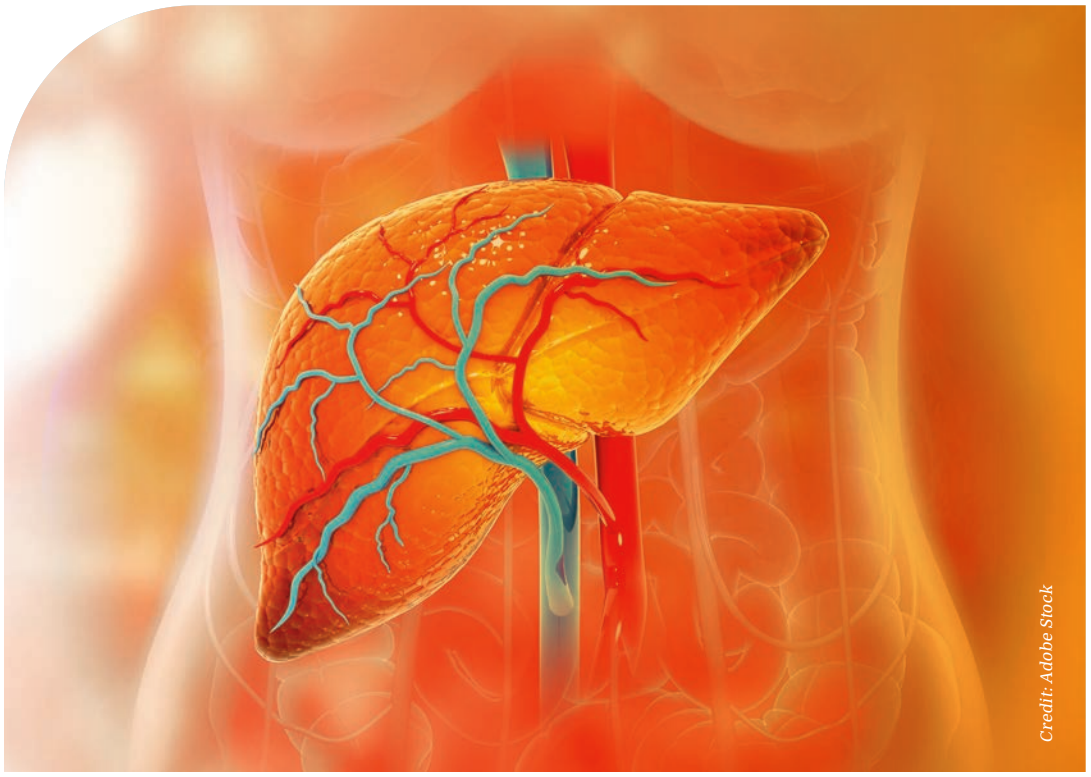
# GI&Hepatology News

American Gastroenterological Association's official newspaper
May 2026 | news.gastro.org

Credit: Adobe Stock

## AGA updates MASLD care pathway

A two-tier strategy is recommended using noninvasive tests to identify patients who require specialty evaluation.

By Doug Brunk

A newly updated AGA clinical care pathway outlines a streamlined, stepwise approach to screening, risk stratification, and treatment of metabolic dysfunction–associated steatotic liver disease (MASLD), emphasizing broader screening of high-risk patients and integrating newly approved pharmacologic therapies.

MASLD — formerly known as nonalcoholic fatty liver disease — affects about 30% of US adults and up to 65% of people with type 2 diabetes, making it one of the most common liver conditions seen in clinical practice. The updated pathway, published in *Gastroenterology* and developed by a multidisciplinary panel convened by AGA, reflects new disease nomenclature, advances in noninvasive testing, and the emergence of FDA-approved therapies for metabolic dysfunction–associated steatohepatitis (MASH).

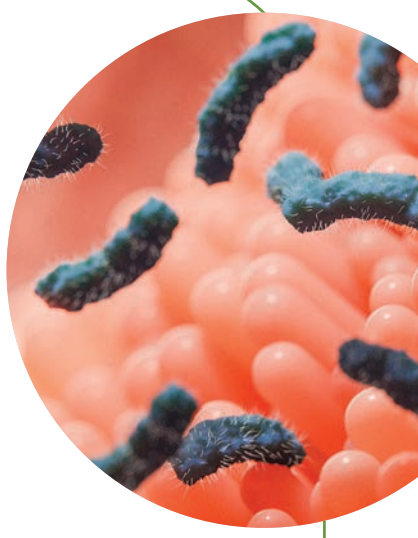
The pathway is designed for use across multiple specialties, including primary care, endocrinology, cardiology, and gastroenterology/hepatology, where most patients with MASLD are evaluated and managed.

### Expanded screening for high-risk groups

A revision of the 2021 version, the pathway prioritizes identifying patients at risk for clinically significant liver fibrosis, defined as stage F2 or higher, which is the strongest predictor of liver-related outcomes.

Continues · Page 16

### AGA launches patient-focused IBD Drug Guide

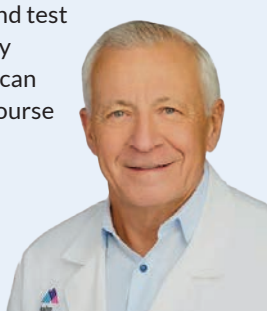


At the heart of the IBD Drug Guide is a structured framework that evaluates therapies based on three key factors: safety, efficacy, and convenience. Users complete a brief, two-minute quiz that captures disease severity, treatment goals, and personal preferences.

Read More • Page 9

### The push to prevent Crohn's disease

Can Crohn's disease be stopped before it starts? A global effort is underway to predict risk, identify silent disease years before symptoms, and test whether early intervention can change the course of IBD.



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MEM23-012

# SHIFT WHEN YOU SWITCH

## TO RINVOQ

**For TNFi-IR patients or if a TNFi is clinically inadvisable**

**INDICATIONS**[1]

**RINVOQ is indicated for the treatment of adults with:**

- **Moderately to severely active Crohn's disease (CD)** who have had an inadequate response or intolerance to one or more tumor necrosis factor (TNF) blockers. If TNF blockers are clinically inadvisable, patients should have received at least one approved systemic therapy prior to use of RINVOQ.
- **Moderately to severely active ulcerative colitis (UC)** who have had an inadequate response or intolerance to one or more TNF blockers. If TNF blockers are clinically inadvisable, patients should have received at least one approved systemic therapy prior to use of RINVOQ.

**Limitations of Use:** RINVOQ is not recommended for use in combination with other Janus kinase (JAK) inhibitors, biological therapies for CD or UC, or with potent immunosuppressants such as azathioprine and cyclosporine.

**Please see additional Important Safety Information for RINVOQ, including BOXED WARNING on Serious Infections, Mortality, Malignancies, Major Adverse Cardiovascular Events, and Thrombosis, on the following pages of this advertisement.**

**Please see Brief Summary of full Prescribing Information on the following pages of this advertisement.**

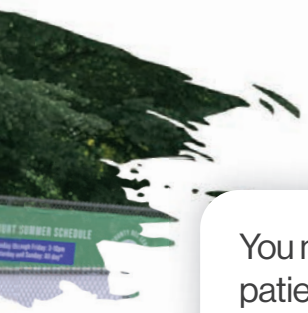
For adults with moderate to severe Crohn's disease (CD) or ulcerative colitis (UC) after inadequate response to a TNFi or another approved systemic therapy if a TNFi is clinically inadvisable[1]

# EXPANDED INDICATIONS in Crohn's and UC[1]

RINVOQ®
upadacitinib

## ALSO AVAILABLE AFTER ANY BIOLOGIC OR ANOTHER APPROVED SYSTEMIC THERAPY

## if a TNFi is clinically inadvisable



You may already be familiar with RINVOQ as a treatment option when treating your adult Crohn's and UC patients who have had an inadequate response or intolerance to a TNFi. RINVOQ can also be used after any first-line biologic or another approved systemic therapy if a TNFi is clinically inadvisable.

**Ultimately, the determination of what is *clinically inadvisable* rests with the treating healthcare professionals, based on their medical judgment and the individual needs of each patient.**

## DO YOU HAVE PATIENTS WHO MAY BE RINVOQ READY?

## VISIT RINVOQHCP.COM/GASTROENTEROLOGY TO LEARN MORE

TNFi=tumor necrosis factor inhibitor.

**SAFETY CONSIDERATIONS[1]**

**Serious Infections:** RINVOQ-treated patients are at increased risk of serious bacterial (including tuberculosis [TB]), fungal, viral, and opportunistic infections leading to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants, such as methotrexate or corticosteroids.

**Mortality:** A higher rate of all-cause mortality, including sudden cardiovascular (CV) death, was observed with a Janus kinase inhibitor (JAKi) in a study comparing another JAKi with tumor necrosis factor (TNF) blockers in rheumatoid arthritis (RA) patients ≥50 years with ≥1 CV risk factor.

**Malignancies:** Malignancies have occurred in RINVOQ-treated patients. A higher rate of lymphomas and lung cancer (in current or past smokers) was observed with another JAKi when compared with TNF blockers in RA patients.

**Major Adverse Cardiovascular Events:** A higher rate of CV death, myocardial infarction, and stroke was observed with a JAKi in a study comparing another JAKi with TNF blockers in RA patients ≥50 years with ≥1 CV risk factor. History of smoking increases risk.

**Thromboses:** Deep venous thrombosis, pulmonary embolism, and arterial thrombosis have occurred in patients treated for inflammatory conditions with JAK inhibitors, including RINVOQ. A higher rate of thrombosis was observed with another JAKi when compared with TNF blockers in RA patients.

**Hypersensitivity:** RINVOQ is contraindicated in patients with hypersensitivity to RINVOQ or its excipients.

**Other Serious Adverse Reactions:** Hypersensitivity Reactions, Gastrointestinal Perforations, Laboratory Abnormalities, and Embryo-Fetal Toxicity.

## IMPORTANT SAFETY INFORMATION[1]

## SERIOUS INFECTIONS

**Patients treated with RINVOQ are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants, such as methotrexate or corticosteroids. If a serious infection develops, interrupt RINVOQ until the infection is controlled.**

**Reported infections include:**

- **Active tuberculosis (TB), which may present with pulmonary or extrapulmonary disease. Test patients for latent TB before RINVOQ use and during therapy. Consider treatment for latent TB infection prior to RINVOQ use.**
- **Invasive fungal infections, including cryptococcosis and pneumocystosis.**
- **Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.**

**Carefully consider the risks and benefits of treatment with RINVOQ prior to initiating therapy in patients with chronic or recurrent infection. Monitor patients closely for the development of signs and symptoms of infection during and after treatment with RINVOQ, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy.**

## MORTALITY

**In a large, randomized, postmarketing safety study comparing another Janus kinase (JAK) inhibitor with tumor necrosis factor (TNF) blockers in rheumatoid arthritis (RA) patients ≥50 years old with at least one cardiovascular (CV) risk factor, a higher rate of all-cause mortality, including sudden CV death, was observed with the JAK inhibitor.** Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with RINVOQ.

## MALIGNANCIES

**Lymphoma and other malignancies have been observed in patients treated with RINVOQ.**

**In a large, randomized, postmarketing safety study comparing another JAK inhibitor with TNF blockers in RA patients, a higher rate of malignancies (excluding non-melanoma skin cancer [NMSC]), lymphomas, and lung cancer (in current or past smokers) was observed with the JAK inhibitor. Patients who are current or past smokers are at additional increased risk.**

With RINVOQ, consider the benefits and risks for the individual patient prior to initiating or continuing therapy, particularly in patients with a known malignancy (other than a successfully treated NMSC), patients who develop a malignancy when on treatment, and patients who are current or past smokers. NMSCs have been reported in patients treated with RINVOQ. Periodic skin examination is recommended for patients who are at increased risk for skin cancer. Advise patients to limit sunlight exposure by wearing protective clothing and using sunscreen.

## MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)

**In a large, randomized, postmarketing study comparing another JAK inhibitor with TNF blockers in RA patients ≥50 years old with at least one CV risk factor, a higher rate of MACE (defined as cardiovascular death, myocardial infarction, and stroke) was observed with the JAK inhibitor. Patients who are current or past smokers are at additional increased risk. Discontinue RINVOQ in patients that have experienced a myocardial infarction or stroke.**

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with RINVOQ, particularly in patients who are current or past smokers and patients with other CV risk factors. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

## THROMBOSIS

**Thromboses, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis, have occurred in patients treated for inflammatory conditions with JAK inhibitors, including RINVOQ. Many of these adverse events were serious and some resulted in death.**

**In a large, randomized, postmarketing study comparing another JAK inhibitor to TNF blockers in RA patients ≥50 years old with at least one CV risk factor, a higher rate of thrombosis was observed with the JAK inhibitor. Avoid RINVOQ in patients at risk. Patients with symptoms of thrombosis should discontinue RINVOQ and be promptly evaluated.**

## HYPERSENSITIVITY

RINVOQ is **contraindicated** in patients with known hypersensitivity to upadacitinib or any of its excipients. Serious hypersensitivity reactions, such as anaphylaxis and angioedema, were reported in patients receiving RINVOQ in clinical trials. If a clinically significant hypersensitivity reaction occurs, discontinue RINVOQ and institute appropriate therapy.

## GASTROINTESTINAL PERFORATIONS

Gastrointestinal (GI) perforations have been reported in clinical trials with RINVOQ. Monitor RINVOQ-treated patients who may be at risk for GI perforation (e.g., patients with a history of diverticulitis and patients taking NSAIDs or corticosteroids). Promptly evaluate patients presenting with new onset abdominal pain for early identification of GI perforation.

## LABORATORY ABNORMALITIES

**Neutropenia**

Treatment with RINVOQ was associated with an increased incidence of neutropenia (absolute neutrophil count [ANC] <1000 cells/mm$^3$). Treatment with RINVOQ is not recommended in patients with an ANC <1000 cells/mm$^3$. Evaluate neutrophil counts at baseline and thereafter according to routine patient management.

**Lymphopenia**

Absolute lymphocyte counts (ALC) <500 cells/mm$^3$ were reported in RINVOQ-treated patients. Treatment with RINVOQ is not recommended in patients with an ALC <500 cells/mm$^3$. Evaluate at baseline and thereafter according to routine patient management.

**Anemia**

Decreases in hemoglobin levels to <8 g/dL were reported in RINVOQ-treated patients. Treatment should not be initiated or should be interrupted in patients with hemoglobin levels <8 g/dL. Evaluate at baseline and thereafter according to routine patient management.

**Lipids**

Treatment with RINVOQ was associated with increases in lipid parameters, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. Manage patients according to clinical guidelines for the management of hyperlipidemia. Evaluate patients 12 weeks after initiation of treatment and thereafter according to the clinical guidelines for hyperlipidemia.

**Liver enzyme elevations**

Treatment with RINVOQ was associated with increased incidence of liver enzyme elevation compared to placebo. Evaluate at baseline and thereafter according to routine patient management. Prompt investigation of the cause of liver enzyme elevation is recommended to identify potential cases of drug-induced liver injury. If increases in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) are observed during routine patient management and drug-induced liver injury is suspected, RINVOQ should be interrupted until this diagnosis is excluded.

## EMBRYO-FETAL TOXICITY

Based on findings in animal studies, RINVOQ may cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with RINVOQ and for 4 weeks after the final dose. Verify pregnancy status of females of reproductive potential prior to starting treatment with RINVOQ.

## VACCINATION

Avoid use of live vaccines during, or immediately prior to, RINVOQ therapy. Prior to initiating RINVOQ, patients should be brought up to date on all immunizations, including prophylactic varicella zoster or herpes zoster vaccinations, in agreement with current immunization guidelines.

## MEDICATION RESIDUE IN STOOL

Reports of medication residue in stool or ostomy output have occurred in patients taking RINVOQ. Most reports described anatomic or functional GI conditions with shortened GI transit times. Instruct patients to contact their healthcare provider if medication residue is observed repeatedly. Monitor patients clinically and consider alternative treatment if there is an inadequate therapeutic response.

## LACTATION

There are no data on the presence of RINVOQ in human milk, the effects on the breastfed infant, or the effects on milk production. Available data in animals have shown the excretion of RINVOQ in milk. Advise patients that breastfeeding is not recommended during treatment with RINVOQ and for 6 days after the last dose.

## HEPATIC IMPAIRMENT

RINVOQ is not recommended for use in patients with severe hepatic impairment.

## ADVERSE REACTIONS

The most common adverse reactions in RINVOQ clinical trials were upper respiratory tract infections, herpes zoster, herpes simplex, bronchitis, nausea, cough, pyrexia, acne, headache, peripheral edema, increased blood creatine phosphokinase, hypersensitivity, folliculitis, abdominal pain, increased weight, influenza, fatigue, neutropenia, myalgia, influenza-like illness, elevated liver enzymes, rash, and anemia.

Inform patients that retinal detachment has been reported in clinical trials with RINVOQ. Advise patients to immediately inform their healthcare provider if they develop any sudden changes in vision while receiving RINVOQ.

**Dosage Forms and Strengths:** RINVOQ is available in 15 mg, 30 mg, and 45 mg extended-release tablets.

**Please see Brief Summary of full Prescribing Information on the following pages of this advertisement.**

**Reference: 1.** RINVOQ [package insert]. North Chicago, IL: AbbVie Inc.

abbvie

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US-RNQG-260002

RINVOQ®
upadacitinib

# **RINVOQ®** (RIN-VOKE) (upadacitinib) extended-release tablets, for oral use
# **RINVOQ® LQ** (RIN-VOKE) (upadacitinib) oral solution

**PROFESSIONAL BRIEF SUMMARY**
**CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION**

**WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS, and THROMBOSIS**

**SERIOUS INFECTIONS**

**Patients treated with RINVOQ/RINVOQ LQ are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions, Adverse Reactions]*. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.**

**If a serious infection develops, interrupt RINVOQ/RINVOQ LQ until the infection is controlled.**

**Reported infections include:**

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before RINVOQ/RINVOQ LQ use and during therapy. Treatment for latent infection should be considered prior to RINVOQ/RINVOQ LQ use.**
- **Invasive fungal infections, including cryptococcosis and pneumocystosis.**
- **Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.**

**The risks and benefits of treatment with RINVOQ/RINVOQ LQ should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.**

**Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with RINVOQ/RINVOQ LQ, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy *[see Warnings and Precautions]*.**

**MORTALITY**

**In a large, randomized, postmarketing safety study in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor comparing another Janus kinase (JAK) inhibitor to tumor necrosis factor (TNF) blockers, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed with the JAK inhibitor *[see Warnings and Precautions]*.**

**MALIGNANCIES**

**Lymphoma and other malignancies have been observed in patients treated with RINVOQ. In RA patients treated with another JAK inhibitor, a higher rate of malignancies (excluding non-melanoma skin cancer (NMSC)) was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk *[see Warnings and Precautions]*.**

**MAJOR ADVERSE CARDIOVASCULAR EVENTS**

**In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with another JAK inhibitor, a higher rate of major adverse cardiovascular events (MACE) (defined as cardiovascular death, myocardial infarction, and stroke), was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk. Discontinue RINVOQ/RINVOQ LQ in patients that have experienced a myocardial infarction or stroke *[see Warnings and Precautions]*.**

**THROMBOSIS**

**Thromboses, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis, have occurred in patients treated for inflammatory conditions with JAK inhibitors, including RINVOQ. Many of these adverse events were serious and some resulted in death. In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with another JAK inhibitor, a higher rate of thrombosis was observed when compared with TNF blockers. Avoid RINVOQ/RINVOQ LQ in patients at risk. Patients with symptoms of thrombosis should discontinue RINVOQ/RINVOQ LQ and be promptly evaluated *[see Warnings and Precautions]*.**

## INDICATIONS AND USAGE

### Rheumatoid Arthritis

RINVOQ® is indicated for the treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more TNF blockers.

- Limitations of Use: RINVOQ is not recommended for use in combination with other JAK inhibitors, biologic disease-modifying antirheumatic drugs (DMARDs), or with potent immunosuppressants such as azathioprine and cyclosporine.

### Ulcerative Colitis

RINVOQ is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response or intolerance to one or more TNF blockers. If TNF blockers are clinically inadvisable, patients should have received at least one approved systemic therapy prior to use of RINVOQ.

- Limitations of Use: RINVOQ is not recommended for use in combination with other JAK inhibitors, biological therapies for UC, or with potent immunosuppressants such as azathioprine and cyclosporine.

### Crohn's Disease

RINVOQ is indicated for the treatment of adult patients with moderately to severely active Crohn's disease (CD) who have had an inadequate response or intolerance to one or more TNF blockers. If TNF blockers are clinically inadvisable, patients should have received at least one approved systemic therapy prior to use of RINVOQ.

- Limitations of Use: RINVOQ is not recommended for use in combination with other JAK inhibitors, biological therapies for CD, or with potent immunosuppressants such as azathioprine and cyclosporine.

## CONTRAINDICATIONS

RINVOQ/RINVOQ LQ is contraindicated in patients with known hypersensitivity to upadacitinib or any of its excipients *[see Warnings and Precautions]*.

## WARNINGS AND PRECAUTIONS

### Serious Infections

Serious and sometimes fatal infections have been reported in patients receiving RINVOQ. The most frequent serious infections reported with RINVOQ included pneumonia and cellulitis *[see Adverse Reactions]*. Among opportunistic infections, tuberculosis, multidermatomal herpes zoster, oral/esophageal candidiasis, and cryptococcosis, were reported with RINVOQ. A higher rate of serious infections was observed with RINVOQ 30 mg compared to RINVOQ 15 mg.

Avoid use of RINVOQ/RINVOQ LQ in patients with an active, serious infection, including localized infections. Consider the risks and benefits of treatment prior to initiating RINVOQ/RINVOQ LQ in patients:

- with chronic or recurrent infection
- who have been exposed to tuberculosis
- with a history of a serious or an opportunistic infection
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or
- with underlying conditions that may predispose them to infection.

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with RINVOQ/RINVOQ LQ. Interrupt RINVOQ/RINVOQ LQ if a patient develops a serious or opportunistic infection.

A patient who develops a new infection during treatment with RINVOQ/RINVOQ LQ should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, the patient should be closely monitored, and RINVOQ/RINVOQ LQ should be interrupted if the patient is not responding to antimicrobial therapy. RINVOQ/RINVOQ LQ may be resumed once the infection is controlled.

Tuberculosis

Evaluate and test patients for latent and active tuberculosis (TB) infection prior to administration of RINVOQ/RINVOQ LQ. Patients with latent TB should be treated with standard antimycobacterial therapy before initiating RINVOQ/RINVOQ LQ. RINVOQ/RINVOQ LQ should not be given to patients with active TB. Consider anti-TB therapy prior to initiation of RINVOQ/RINVOQ LQ in patients with previously untreated latent TB or active TB in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent TB but who have risk factors for TB infection.

Consultation with a physician with expertise in the treatment of TB is recommended to aid in the decision about whether initiating anti-TB therapy is appropriate for an individual patient.

During RINVOQ/RINVOQ LQ use, monitor patients for the development of signs and symptoms of TB, including patients who tested negative for latent TB infection prior to initiating therapy.

Viral Reactivation

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster) and hepatitis B virus reactivation, were reported in clinical trials with RINVOQ *[see Adverse Reactions]*. The risk of herpes zoster appears to be higher in patients treated with RINVOQ in Japan. If a patient develops herpes zoster, consider temporarily interrupting RINVOQ/RINVOQ LQ until the episode resolves.

Screening for viral hepatitis and monitoring for reactivation should be performed in accordance with clinical guidelines before starting and during therapy with RINVOQ/RINVOQ LQ. Patients who were positive for hepatitis C antibody and hepatitis C virus RNA, were excluded from clinical trials. Patients who were positive for hepatitis B surface antigen or hepatitis B virus DNA were excluded from clinical trials. However, cases of hepatitis B reactivation were still reported in patients enrolled in the Phase 3 trials of RINVOQ. If hepatitis B virus DNA is detected while receiving RINVOQ/RINVOQ LQ, a liver specialist should be consulted.

### Mortality

In a large, randomized, postmarketing safety study of another JAK inhibitor in RA patients 50 years of age and older with at least one cardiovascular risk factor, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed in patients treated with the JAK inhibitor compared with TNF blockers.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with RINVOQ/RINVOQ LQ.

### Malignancy and Lymphoproliferative Disorders

Malignancies, including lymphomas, were observed in clinical trials of RINVOQ *[see Adverse Reactions]*.

In a large, randomized, postmarketing safety study of another JAK inhibitor in RA patients, a higher rate of malignancies (excluding NMSC) was observed in patients treated with the JAK inhibitor compared to those treated with TNF blockers. A higher rate of lymphomas was observed in patients treated with the JAK inhibitor compared to those treated with TNF blockers. A higher rate of lung cancers was observed in current or past smokers treated with the JAK inhibitor compared to those treated with TNF blockers. In this study, current or past smokers had an additional increased risk of overall malignancies.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with RINVOQ/RINVOQ LQ, particularly in patients with a known malignancy (other than a successfully treated NMSC), patients who develop a malignancy when on treatment, and patients who are current or past smokers.

Non-Melanoma Skin Cancer

NMSCs have been reported in patients treated with RINVOQ. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

Exposure to sunlight and UV light should be limited by wearing protective clothing and using a broad-spectrum sunscreen.

### Major Adverse Cardiovascular Events

In a large, randomized, postmarketing safety study of another JAK inhibitor in RA patients 50 years of age and older with at least one cardiovascular risk factor, a higher rate of major adverse cardiovascular events (MACE) defined as cardiovascular death, non-fatal myocardial infarction (MI), and non-fatal stroke was observed with the JAK inhibitor compared to those treated with TNF blockers. Patients who are current or past smokers are at additional increased risk.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with RINVOQ/RINVOQ LQ, particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur. Discontinue RINVOQ/RINVOQ LQ in patients that have experienced a myocardial infarction or stroke.

### Thrombosis

Thromboses, including deep venous thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis, have occurred in patients treated for inflammatory conditions with JAK inhibitors, including RINVOQ. Many of these adverse events were serious and some resulted in death *[see Adverse Reactions]*.

In a large, randomized, postmarketing safety study of another JAK inhibitor in RA patients 50 years of age and older with at least one cardiovascular risk factor, higher rates of overall thrombosis, DVT, and PE were observed compared to those treated with TNF blockers.

If symptoms of thrombosis occur, patients should discontinue RINVOQ/RINVOQ LQ and be evaluated promptly and treated appropriately. Avoid RINVOQ/RINVOQ LQ in patients that may be at increased risk of thrombosis.

### Hypersensitivity Reactions

Serious hypersensitivity reactions such as anaphylaxis and angioedema were reported in patients receiving RINVOQ in clinical trials. If a clinically significant hypersensitivity reaction occurs, discontinue RINVOQ/RINVOQ LQ and institute appropriate therapy *[see Adverse Reactions]*.

### Gastrointestinal Perforations

Gastrointestinal perforations have been reported in clinical trials with RINVOQ *[see Adverse Reactions]*.

Monitor RINVOQ/RINVOQ LQ-treated patients who may be at risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis and those taking concomitant medications including NSAIDs or corticosteroids). Evaluate promptly patients presenting with new onset abdominal pain for early identification of gastrointestinal perforation.

### Laboratory Abnormalities

Neutropenia

Treatment with RINVOQ was associated with an increased incidence of neutropenia (ANC less than 1000 cells/mm$^3$).

Evaluate neutrophil counts at baseline and thereafter according to routine patient management. Avoid RINVOQ/RINVOQ LQ initiation and interrupt RINVOQ/RINVOQ LQ treatment in patients with a low neutrophil count (i.e., ANC less than 1000 cells/mm$^3$).

Lymphopenia

ALC less than 500 cells/mm$^3$ were reported in RINVOQ-treated patients in clinical trials.

Evaluate lymphocyte counts at baseline and thereafter according to routine patient management. Avoid RINVOQ/RINVOQ LQ initiation or interrupt RINVOQ/RINVOQ LQ treatment in patients with a low lymphocyte count (i.e., less than 500 cells/mm$^3$).

Anemia

Decreases in hemoglobin levels to less than 8 g/dL were reported in RINVOQ-treated patients in clinical trials.

Evaluate hemoglobin at baseline and thereafter according to routine patient management. Avoid RINVOQ/RINVOQ LQ initiation or interrupt RINVOQ/RINVOQ LQ treatment in patients with a low hemoglobin level (i.e., less than 8 g/dL).

Lipids

Treatment with RINVOQ was associated with increases in lipid parameters, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol *[see Adverse Reactions]*. Elevations in LDL cholesterol decreased to pre-treatment levels in response to statin therapy. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined.

Assess lipid parameters approximately 12 weeks after initiation of treatment, and thereafter according to the clinical guidelines for hyperlipidemia. Manage patients according to clinical guidelines for the management of hyperlipidemia.

Liver Enzyme Elevations

Treatment with RINVOQ was associated with increased incidence of liver enzyme elevations compared to treatment with placebo.

Evaluate liver enzymes at baseline and thereafter according to routine patient management. Prompt investigation of the cause of liver enzyme elevation is recommended to identify potential cases of drug-induced liver injury.

If increases in ALT or AST are observed during routine patient management and drug-induced liver injury is suspected, RINVOQ/RINVOQ LQ should be interrupted until this diagnosis is excluded.

### Embryo-Fetal Toxicity

Based on findings in animal studies, RINVOQ/RINVOQ LQ may cause fetal harm when administered to a pregnant woman. Administration of upadacitinib to rats and rabbits during organogenesis caused increases in fetal malformations. Verify the pregnancy status of patients of reproductive potential prior to starting treatment. Advise females of reproductive potential of the potential risk to the fetus and to use effective contraception during treatment with RINVOQ/RINVOQ LQ and for 4 weeks following completion of therapy *[see Use in Specific Populations]*.

### Vaccinations

Avoid use of live vaccines during or immediately prior to RINVOQ/RINVOQ LQ therapy initiation. Prior to initiating RINVOQ/RINVOQ LQ treatment, it is recommended that patients be brought up to date with all immunizations, including prophylactic varicella zoster or herpes zoster vaccinations, in agreement with current immunization guidelines.

### Medication Residue in Stool

Reports of medication residue in stool or ostomy output have occurred in patients taking RINVOQ. Most reports described anatomic (e.g., ileostomy, colostomy, intestinal resection) or functional gastrointestinal conditions with shortened gastrointestinal transit times. Instruct patients to contact their healthcare provider if medication residue is observed repeatedly. Monitor patients clinically and consider alternative treatment if there is an inadequate therapeutic response.

## ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Serious Infections *[see Warnings and Precautions]*
- Mortality *[see Warnings and Precautions]*
- Malignancy and Lymphoproliferative Disorders *[see Warnings and Precautions]*
- Major Adverse Cardiovascular Events *[see Warnings and Precautions]*
- Thrombosis *[see Warnings and Precautions]*
- Hypersensitivity Reactions *[see Warnings and Precautions]*
- Gastrointestinal Perforations *[see Warnings and Precautions]*
- Laboratory Abnormalities *[see Warnings and Precautions]*

### Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions in Patients with Rheumatoid Arthritis

A total of 3833 adult patients with rheumatoid arthritis were treated with RINVOQ 15 mg or upadacitinib 30 mg tablets once daily in the Phase 3 clinical trials of whom 2806 were exposed for at least one year.

Patients could advance or switch to RINVOQ 15 mg from placebo, or be rescued to RINVOQ from active comparator or placebo from as early as Week 12 depending on the trial design.

A total of 2630 patients received at least 1 dose of RINVOQ 15 mg, of whom 1860 were exposed for at least one year. In trials RA-I, RA-II, RA-III and RA-V, 1213 patients received at least 1 dose of RINVOQ 15 mg, of which 986 patients were exposed for at least one year, and 1203 patients received at least 1 dose of upadacitinib 30 mg, of which 946 were exposed for at least one year.

**Table 1: Adverse Reactions Reported in ≥ 1% of Rheumatoid Arthritis Patients Treated with RINVOQ 15 mg in Placebo-controlled Trials**

| Adverse Reaction | Placebo N = 1042 (%) | RINVOQ 15 mg N = 1035 (%) |
|---|---|---|
| Upper respiratory tract infection (URTI)* | 9.5 | 13.5 |
| Nausea | 2.2 | 3.5 |
| Cough | 1.0 | 2.2 |
| Pyrexia | 0 | 1.2 |

*URTI includes: acute sinusitis, laryngitis, nasopharyngitis, oropharyngeal pain, pharyngitis, pharyngotonsillitis, rhinitis, sinusitis, tonsillitis, viral upper respiratory tract infection

Other adverse reactions reported in less than 1% of patients in the RINVOQ 15 mg group and at a higher rate than in the placebo group through Week 12 included pneumonia, herpes zoster, herpes simplex (includes oral herpes), and oral candidiasis.

Four integrated datasets are presented in the Specific Adverse Reaction section:

Placebo-controlled Trials: Trials RA-III, RA-IV, and RA-V were integrated to represent safety through 12/14 weeks for placebo (n=1042) and RINVOQ 15 mg (n=1035). Trials RA-III and RA-V were integrated to represent safety through 12 weeks for placebo (n=390), RINVOQ 15 mg (n=385), and upadacitinib 30 mg (n=384). Trial RA-IV did not include the 30 mg dose and, therefore, safety data for upadacitinib 30 mg can only be compared with placebo and RINVOQ 15 mg rates from pooling trials RA-III and RA-V.

MTX-controlled Trials: Trials RA-I and RA-II were integrated to represent safety through 12/14 weeks for MTX (n=530), RINVOQ 15 mg (n=534), and upadacitinib 30 mg (n=529).

12-Month Exposure Dataset: Trials RA-I, II, III, and V were integrated to represent the long-term safety of RINVOQ 15 mg (n=1213) and upadacitinib 30 mg (n=1203).

Exposure adjusted incidence rates were adjusted by trial for all the adverse events reported in this section.

*Specific Adverse Reactions*

*Infections*

Placebo-controlled Trials: In RA-III, RA-IV, and RA-V, infections were reported in 218 patients (95.7 per 100 patient-years) treated with placebo and 284 patients (127.8 per 100 patient-years) treated with RINVOQ 15 mg. In RA-III and RA-V, infections were reported in 99 patients (136.5 per 100 patient-years) treated with placebo, 118 patients (164.5 per 100 patient-years) treated with RINVOQ 15 mg, and 126 patients (180.3 per 100 patient-years) treated with upadacitinib 30 mg.

MTX-controlled Trials: Infections were reported in 127 patients (119.5 per 100 patient-years) treated with MTX monotherapy, 104 patients (91.8 per 100 patient-years) treated with RINVOQ 15 mg monotherapy, and 128 patients (115.1 per 100 patient-years) treated with upadacitinib 30 mg monotherapy.

12-Month Exposure Dataset: Infections were reported in 615 patients (83.8 per 100 patient-years) treated with RINVOQ 15 mg and 674 patients (99.7 per 100 patient-years) treated with upadacitinib 30 mg.

*Serious Infections*

Placebo-controlled Trials: In RA-III, RA-IV, and RA-V, serious infections were reported in 6 patients (2.3 per 100 patient-years) treated with placebo, and 12 patients (4.6 per 100 patient-years) treated with RINVOQ 15 mg. In RA-III and RA-V, serious infections were reported in 1 patient (1.2 per 100 patient-years) treated with placebo, 2 patients (2.3 per 100 patient-years) treated with RINVOQ 15 mg, and 7 patients (8.2 per 100 patient-years) treated with upadacitinib 30 mg.

MTX-controlled Trials: Serious infections were reported in 2 patients (1.6 per 100 patient-years) treated with MTX monotherapy, 3 patients (2.4 per 100 patient-years) treated with RINVOQ 15 mg monotherapy, and 8 patients (6.4 per 100 patient-years) treated with upadacitinib 30 mg monotherapy.

12-Month Exposure Dataset: Serious infections were reported in 38 patients (3.5 per 100 patient-years) treated with RINVOQ 15 mg and 59 patients (5.6 per 100 patient-years) treated with upadacitinib 30 mg.

The most frequently reported serious infections were pneumonia and cellulitis.

*Tuberculosis*

Placebo-controlled Trials and MTX-controlled Trials: In the placebo-controlled period, there were no active cases of tuberculosis reported in the placebo, RINVOQ 15 mg, and upadacitinib 30 mg groups. In the MTX-controlled period, there were no active cases of tuberculosis reported in the MTX monotherapy, RINVOQ 15 mg monotherapy, and upadacitinib 30 mg monotherapy groups.

12-Month Exposure Dataset: Active tuberculosis was reported for 2 patients treated with RINVOQ 15 mg and 1 patient treated with upadacitinib 30 mg. Cases of extra-pulmonary tuberculosis were reported.

*Opportunistic Infections (excluding tuberculosis)*

Placebo-controlled Trials: In RA-III, RA-IV, and RA-V, opportunistic infections were reported in 3 patients (1.2 per 100 patient-years) treated with placebo, and 5 patients (1.9 per 100 patient-years) treated with RINVOQ 15 mg. In RA-III and RA-V, opportunistic infections were reported in 1 patient (1.2 per 100 patient-years) treated with placebo, 2 patients (2.3 per 100 patient-years) treated with RINVOQ 15 mg, and 6 patients (7.1 per 100 patient-years) treated with upadacitinib 30 mg.

MTX-controlled Trials: Opportunistic infections were reported in 1 patient (0.8 per 100 patient-years) treated with MTX monotherapy, 0 patients treated with RINVOQ 15 mg monotherapy, and 4 patients (3.2 per 100 patient-years) treated with upadacitinib 30 mg monotherapy.

12-Month Exposure Dataset: Opportunistic infections were reported in 7 patients (0.6 per 100 patient-years) treated with RINVOQ 15 mg and 15 patients (1.4 per 100 patient-years) treated with upadacitinib 30 mg.

*Malignancies*

Placebo-controlled Trials: In RA-III, RA-IV, and RA-V, malignancies excluding NMSC were reported in 1 patient (0.4 per 100 patient-years) treated with placebo, and 1 patient (0.4 per 100 patient-years) treated with RINVOQ 15 mg. In RA-III and RA-V, malignancies excluding NMSC were reported in 0 patients treated with placebo, 1 patient (1.1 per 100 patient-years) treated with RINVOQ 15 mg, and 3 patients (3.5 per 100 patient-years) treated with upadacitinib 30 mg.

MTX-controlled Trials: Malignancies excluding NMSC were reported in 1 patient (0.8 per 100 patient-years) treated with MTX monotherapy, 3 patients (2.4 per 100 patient-years) treated with RINVOQ 15 mg monotherapy, and 0 patients treated with upadacitinib 30 mg monotherapy.

12-Month Exposure Dataset: Malignancies excluding NMSC were reported in 13 patients (1.2 per 100 patient-years) treated with RINVOQ 15 mg and 14 patients (1.3 per 100 patient-years) treated with upadacitinib 30 mg.

*Gastrointestinal Perforations*

Placebo-controlled Trials: There were no gastrointestinal perforations (based on medical review) reported in patients treated with placebo, RINVOQ 15 mg, and upadacitinib 30 mg.

MTX-controlled Trials: There were no cases of gastrointestinal perforations reported in the MTX and RINVOQ 15 mg group through 12/14 weeks. Two cases of gastrointestinal perforations were observed in the upadacitinib 30 mg group.

12-Month Exposure Dataset: Gastrointestinal perforations were reported in 1 patient treated with RINVOQ 15 mg and 4 patients treated with upadacitinib 30 mg.

*Thrombosis*

Placebo-controlled Trials: In RA-IV, venous thrombosis (pulmonary embolism or deep vein thrombosis) was observed in 1 patient treated with placebo and 1 patient treated with RINVOQ 15 mg. In RA-V, venous thrombosis was observed in 1 patient treated with RINVOQ 15 mg. There were no observed cases of venous thrombosis reported in RA-III. No cases of arterial thrombosis were observed through 12/14 weeks.

MTX-controlled Trials: In RA-II, venous thrombosis was observed in 0 patients treated with MTX monotherapy, 1 patient treated with RINVOQ 15 mg monotherapy and 0 patients treated with upadacitinib 30 mg monotherapy through Week 14. In RA-II, no cases of arterial thrombosis were observed through 12/14 weeks. In RA-I, venous thrombosis was observed in 1 patient treated with MTX, 0 patients treated with RINVOQ 15 mg and 1 patient treated with upadacitinib 30 mg through Week 24. In RA-I, arterial thrombosis was observed in 1 patient treated with upadacitinib 30 mg through Week 24.

12-Month Exposure Dataset: Venous thrombosis events were reported in 5 patients (0.5 per 100 patient-years) treated with RINVOQ 15 mg and 4 patients (0.4 per 100 patient-years) treated with upadacitinib 30 mg. Arterial thrombosis events were reported in 0 patients treated with RINVOQ 15 mg and 2 patients (0.2 per 100 patient-years) treated with upadacitinib 30 mg.

*Laboratory Abnormalities*

*Hepatic Transaminase Elevations*

In placebo-controlled trials (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, alanine transaminase (ALT) and aspartate transaminase (AST) elevations ≥ 3 x upper limit of normal (ULN) in at least one measurement were observed in 2.1% and 1.5% of patients treated with RINVOQ 15 mg, and in 1.5% and 0.7% of patients treated with placebo, respectively. In RA-III and RA-V, ALT and AST elevations ≥ 3 x ULN in at least one measurement were observed in 0.8% and 1.0% of patients treated with RINVOQ 15 mg, 1.0% and 0% of patients treated with upadacitinib 30 mg and in 1.3% and 1.0% of patients treated with placebo, respectively.

In MTX-controlled trials, for up to 12/14 weeks, ALT and AST elevations ≥ 3 x ULN in at least one measurement were observed in 0.8% and 0.4% of patients treated with RINVOQ 15 mg, 1.7% and 1.3% of patients treated with upadacitinib 30 mg and in 1.9% and 0.9% of patients treated with MTX, respectively.

*Lipid Elevations*

Upadacitinib treatment was associated with dose-related increases in total cholesterol, triglycerides and LDL cholesterol. Upadacitinib was also associated with increases in HDL cholesterol. Elevations in LDL and HDL cholesterol peaked by Week 8 and remained stable thereafter. In controlled trials, for up to 12/14 weeks, changes from baseline in lipid parameters in patients treated with RINVOQ 15 mg and upadacitinib 30 mg, respectively, are summarized below:

- Mean LDL cholesterol increased by 14.81 mg/dL and 17.17 mg/dL.
- Mean HDL cholesterol increased by 8.16 mg/dL and 9.01 mg/dL.
- The mean LDL/HDL ratio remained stable.
- Mean triglycerides increased by 13.55 mg/dL and 14.44 mg/dL.

*Creatine Phosphokinase Elevations*

In placebo-controlled trials (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, dose-related increases in creatine phosphokinase (CPK) values were observed. CPK elevations > 5 x ULN were reported in 1.0%, and 0.3% of patients over 12/14 weeks in the RINVOQ 15 mg and placebo groups, respectively. Most elevations >5 x ULN were transient and did not require treatment discontinuation. In RA-III and RA-V, CPK elevations > 5 x ULN were observed in 0.3% of patients treated with placebo, 1.6% of patients treated with RINVOQ 15 mg, and none in patients treated with upadacitinib 30 mg.

*Neutropenia*

In placebo-controlled trials (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, dose-related decreases in neutrophil counts, below 1000 cells/mm$^3$ in at least one measurement occurred in 1.1% and <0.1% of patients in the RINVOQ 15 mg and placebo groups, respectively. In RA-III and RA-V, decreases in neutrophil counts below 1000 cells/mm$^3$ in at least one measurement occurred in 0.3% of patients treated with placebo, 1.3% of patients treated with RINVOQ 15 mg, and 2.4% of patients treated with upadacitinib 30 mg. In clinical trials, treatment was interrupted in response to ANC less than 1000 cells/mm$^3$.

*Lymphopenia*

In placebo-controlled trials (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, dose-related decreases in lymphocyte counts below 500 cells/mm$^3$ in at least one measurement occurred in 0.9% and 0.7% of patients in the RINVOQ 15 mg and placebo groups, respectively. In RA-III and RA-V, decreases in lymphocyte counts below 500 cells/mm$^3$ in at least one measurement occurred in 0.5% of patients treated with placebo, 0.5% of patients treated with RINVOQ 15 mg, and 2.4% of patients treated with upadacitinib 30 mg.

*Anemia*

In placebo-controlled trials (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, hemoglobin decreases below 8 g/dL in at least one measurement occurred in <0.1% of patients in both the RINVOQ 15 mg and placebo groups. In RA-III and RA-V, hemoglobin decreases below 8 g/dL in at least one measurement were observed in 0.3% of patients treated with placebo, and none in patients treated with RINVOQ 15 mg and upadacitinib 30 mg.

Adverse Reactions in Patients with Ulcerative Colitis

RINVOQ was studied up to 8 weeks in patients with moderately to severely active ulcerative colitis in two randomized, double-blind, placebo-controlled induction studies (UC-1, UC-2) and a randomized, double-blind, placebo controlled, dose-finding study (UC-4; NCT02819635). Long term safety up to 52-weeks was evaluated in patients who responded to induction therapy in a randomized, double-blind, placebo-controlled maintenance study (UC-3) and a long-term extension study.

In the two induction studies (UC-1, UC-2) and a dose finding study (UC-4), 1097 patients were enrolled of whom 719 patients received RINVOQ 45 mg tablets once daily.

In the maintenance study (UC-3), 746 patients were enrolled of whom 250 patients received RINVOQ 15 mg tablets once daily and 251 patients received RINVOQ 30 mg tablets once daily.

Adverse reactions reported in ≥2% of patients in any treatment arm in the induction and maintenance studies are shown in Tables 2 and 3, respectively.

**Table 2: Adverse Reactions Reported in ≥2% of Patients with Ulcerative Colitis Treated with RINVOQ 45 mg in Placebo-Controlled Induction Studies (UC-1, UC-2 and UC-4)**

| Adverse Reaction | Placebo | RINVOQ 45 mg Once Daily |
|---|---|---|
| | N = 378 (%) | N = 719 (%) |
| Upper respiratory tract infection* | 7 | 9 |
| Acne* | 1 | 6 |
| Increased blood creatine phosphokinase | 1 | 5 |
| Neutropenia* | <1 | 5 |
| Rash* | 1 | 4 |
| Elevated liver enzymes** | 2 | 3 |
| Lymphopenia* | 1 | 3 |
| Folliculitis | 1 | 2 |
| Herpes simplex* | <1 | 2 |

* Composed of several similar terms

** Elevated liver enzymes composed of elevated ALT, AST, GGT, ALP, liver transaminases, hepatic enzymes, bilirubin, drug-induced liver injury and cholestasis.

Other adverse reactions reported in less than 2% of patients in the RINVOQ 45 mg group and at a higher rate than in the placebo group through Week 8 included herpes zoster and pneumonia.

**Table 3: Adverse Reactions Reported in ≥2% of Patients with Ulcerative Colitis Treated with RINVOQ 15 mg or 30 mg in the Placebo-Controlled Maintenance Study (UC-3)[1]**

| Adverse Reaction | Placebo | RINVOQ 15 mg Once Daily | RINVOQ 30 mg Once Daily |
|---|---|---|---|
| | N = 245 (%) | N = 250 (%) | N = 251 (%) |
| Upper respiratory tract infection* | 18 | 17 | 20 |
| Increased blood creatine phosphokinase | 2 | 6 | 8 |
| Pyrexia | 3 | 3 | 6 |
| Neutropenia* | 2 | 3 | 6 |
| Elevated liver enzymes** | 1 | 6 | 4 |
| Rash* | 4 | 5 | 5 |
| Herpes zoster | 0 | 5 | 6 |
| Folliculitis | 2 | 2 | 4 |
| Hypercholesterolemia* | 1 | 2 | 4 |
| Influenza | 1 | 3 | 3 |
| Herpes simplex* | 1 | 2 | 3 |
| Lymphopenia* | 2 | 3 | 2 |
| Hyperlipidemia* | 0 | 2 | 2 |

[1] Patients who were responders to 8 weeks induction therapy with RINVOQ 45 mg once daily

* Composed of several similar terms

** Elevated liver enzymes composed of elevated ALT, AST, GGT, ALP, liver transaminases, hepatic enzymes, bilirubin, drug-induced liver injury, and cholestasis.

The adverse reaction of non-melanoma skin cancer was reported in 1% of patients in the RINVOQ 30 mg group and none of the patients in the RINVOQ 15 mg or placebo group through Week 52.

The safety profile of RINVOQ in the long-term extension study was similar to the safety profile observed in the placebo-controlled induction and maintenance periods.

Overall, the safety profile observed in patients with ulcerative colitis treated with RINVOQ was generally similar to the safety profile in patients with RA and AD.

*Specific Adverse Reactions*

*Serious Infections*

Induction Studies: In UC-1, UC-2, and UC-4, serious infections were reported in 5 patients (8.4 per 100 patient-years) treated with placebo and 9 patients (8.4 per 100 patient-years) treated with RINVOQ 45 mg through 8 weeks.

Placebo-controlled Maintenance Study: In UC-3, serious infections were reported in 8 patients (5.9 events per 100 patient-years) treated with placebo, 9 patients (5.0 events per 100 patient-years) treated with RINVOQ 15 mg, and 8 patients (3.7 events per 100 patient-years) treated with RINVOQ 30 mg through 52 weeks.

*Laboratory Abnormalities*

*Hepatic Transaminase Elevations*

In studies UC-1, UC-2, and UC-4, elevations of ALT to ≥ 3 x ULN in at least one measurement were observed in 1.5% of patients treated with RINVOQ 45 mg, and 0% of patients treated with placebo for 8 weeks. AST elevations to ≥ 3 x ULN occurred in 1.5% of patients treated with RINVOQ 45 mg, and 0.3% of patients treated with placebo. Elevations of ALT to ≥ 5 x ULN occurred in 0.4% of patients treated with RINVOQ 45 mg and 0% of patients treated with placebo.

In UC-3, elevations of ALT to ≥ 3 x ULN in at least one measurement were observed in 4.4% of patients treated with RINVOQ 30 mg, 2% of patients treated with RINVOQ 15 mg, and 1.2% of patients treated with placebo for 52 weeks. Elevations of AST to ≥ 3 x ULN in at least one measurement were observed in 2% of patients treated with RINVOQ 30 mg, 1.6% of patients treated with RINVOQ 15 mg and 0.4% of patients treated with placebo. Elevations of ALT to ≥ 5 x ULN were observed in 1.2% of patients treated with 30 mg, 0.4% of patients treated with 15 mg, and 0.4% of patients treated with placebo.

Overall, laboratory abnormalities observed in patients with ulcerative colitis treated with RINVOQ were similar to those described in patients with RA.

Adverse Reactions in Patients with Crohn's Disease

RINVOQ was studied up to 12 weeks in patients with moderately to severely active CD in two randomized, double-blind, placebo-controlled induction studies (CD-1, CD-2). Long term safety up to 52 weeks was evaluated in patients who responded to induction therapy in a randomized, double-blind, placebo-controlled maintenance study (CD-3), with additional data provided from a long-term extension (LTE) period.

In the two induction studies (CD-1, CD-2), 1021 patients were enrolled, of whom 674 patients received RINVOQ 45 mg tablets once daily during the placebo-controlled period.

In the maintenance study (CD-3), 673 patients were enrolled, of whom 221 patients received RINVOQ 15 mg tablets once daily and 229 patients received RINVOQ 30 mg tablets once daily during the randomized, placebo-controlled period.

Overall, the safety profile observed in patients with Crohn's disease treated with RINVOQ was consistent with the known safety profile for RINVOQ in other indications.

Adverse reactions reported in ≥2% of patients treated with RINVOQ and at a higher rate than placebo in the induction and maintenance studies are shown in Tables 4 and 5, respectively.

**Table 4: Adverse Reactions Reported in ≥2% of Patients with Crohn's Disease Treated with RINVOQ 45 mg in Placebo-Controlled Induction Studies (CD-1 and CD-2)**

| Adverse Reaction | Placebo | RINVOQ 45 mg Once Daily |
|---|---|---|
| | N = 347 (%) | N = 674 (%) |
| Upper respiratory tract infection* | 8 | 13 |
| Anemia* | 6 | 7 |
| Acne* | 2 | 6 |
| Pyrexia | 3 | 4 |
| Increased blood creatine phosphokinase | 1 | 3 |
| Influenza | 1 | 3 |
| Herpes simplex* | 1 | 3 |
| Leukopenia* | 1 | 2 |
| Neutropenia* | <1 | 2 |
| Herpes zoster | 0 | 2 |

* Composed of several similar terms

Adverse reactions reported in less than 2% of patients in the RINVOQ 45 mg group and at a higher rate than in the placebo group through Week 12 included folliculitis, hypercholesterolemia, bronchitis, pneumonia, oral candidiasis, and hyperlipidemia.

**Table 5: Adverse Reactions Reported in ≥2% of Patients with Crohn's Disease Treated with RINVOQ 15 mg or 30 mg in the Placebo-Controlled Maintenance Study (CD-3)[1]**

| Adverse Reaction | Placebo | RINVOQ 15 mg Once Daily | RINVOQ 30 mg Once Daily |
|---|---|---|---|
| | N = 223 (%) | N = 221 (%) | N = 229 (%) |
| Upper respiratory tract infection* | 11 | 14 | 12 |
| Pyrexia | 2 | 3 | 7 |
| Herpes zoster* | 2 | 3 | 5 |
| Headache* | 1 | 3 | 5 |
| Acne* | 3 | 2 | 5 |
| Gastroenteritis* | 2 | 3 | 3 |
| Fatigue | 2 | 3 | 3 |
| Increased blood creatine phosphokinase | 1 | 2 | 3 |
| Elevated liver enzymes[2] | <1 | 2 | 3 |
| Leukopenia* | <1 | 1 | 2 |
| Neutropenia* | <1 | 1 | 2 |
| Bronchitis* | 0 | 1 | 2 |
| Pneumonia* | 1 | 4 | 1 |
| Cough | 2 | 3 | 1 |

[1] Patients who were responders to 12 weeks induction therapy with RINVOQ 45 mg once daily.

[2] Elevated liver enzymes includes alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, transaminases increased, blood bilirubin increased.

* Composed of several similar terms

Adverse reactions reported in less than 2% of patients in the RINVOQ 15 mg or 30 mg group and at a higher rate than in the placebo group through Week 52 included hyperlipidemia, oral candidiasis, and hypercholesterolemia.

The safety profile of RINVOQ in the long-term extension study was similar to the safety profile observed in the placebo-controlled induction and maintenance periods.

*Specific Adverse Reactions*

*Serious Infections*

Induction Studies: In CD-1 and CD-2, serious infections were reported in 6 patients (8 per 100 patient-years) treated with placebo and 13 patients (9 per 100 patient-years) treated with RINVOQ 45 mg through 12 weeks of the placebo-controlled period.

Maintenance Study/LTE: In the long-term placebo-controlled period, serious infections were reported in 10 patients (7 per 100 patient-years) treated with placebo, 7 patients (4 per 100 patient-years) treated with RINVOQ 15 mg, and 13 patients (6 per 100 patient-years) treated with RINVOQ 30 mg.

*Gastrointestinal Perforations*

Induction Studies: During the induction studies in all patients treated with RINVOQ 45 mg (N=938), gastrointestinal perforation was reported in 4 patients (2 per 100 patient-years). In the placebo-controlled induction period, in CD-1 and CD-2, gastrointestinal perforation was reported in no patients treated with placebo (N=347) and 1 patient (1 per 100 patient-years) treated with RINVOQ 45 mg (N=674) through 12 weeks.

Maintenance Study/LTE: In the long-term placebo-controlled period, gastrointestinal perforation was reported in 1 patient (1 per 100 patient-years) treated with placebo, 1 patient (<1 per 100 patient-years) treated with RINVOQ 15 mg, and 1 patient (<1 per 100 patient-years) treated with RINVOQ 30 mg.

Patients who received placebo or RINVOQ 15 mg for maintenance therapy and lost response were treated with rescue RINVOQ 30 mg (N=336). Among these patients, gastrointestinal perforation was reported in 3 patients (1 per 100 patient-years) through long-term treatment.

## DRUG INTERACTIONS

**Strong CYP3A4 Inhibitors**

Upadacitinib exposure is increased when it is co-administered with a strong CYP3A4 inhibitor (such as ketoconazole, clarithromycin, and grapefruit), which may increase the risk of adverse reactions. Monitor patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondylarthritis, pJIA, or giant cell arteritis closely for adverse reactions when co-administering RINVOQ/RINVOQ LQ with strong CYP3A4 inhibitors. Food or drink containing grapefruit should be avoided during treatment with RINVOQ/RINVOQ LQ.

For patients with atopic dermatitis, coadministration of RINVOQ 30 mg once daily with strong CYP3A4 inhibitors is not recommended.

For patients with ulcerative colitis or Crohn's disease taking strong CYP3A4 inhibitors, reduce the RINVOQ induction dosage to 30 mg once daily. The recommended maintenance dosage is 15 mg once daily.

**Strong CYP3A4 Inducers**

Upadacitinib exposure is decreased when it is co-administered with strong CYP3A4 inducers (such as rifampin), which may lead to reduced therapeutic effect. Coadministration of RINVOQ/RINVOQ LQ with strong CYP3A4 inducers is not recommended.

## USE IN SPECIFIC POPULATIONS

**Pregnancy**

Pregnancy Surveillance Program

There is a pregnancy surveillance program for RINVOQ/RINVOQ LQ that monitors pregnancy outcomes in women exposed to RINVOQ/RINVOQ LQ. If RINVOQ/RINVOQ LQ exposure occurs during pregnancy, healthcare providers or patients should report the pregnancy by calling 1-800-633-9110.

Risk Summary

Available data from the pharmacovigilance safety database and postmarketing case reports on use of RINVOQ in pregnant women are not sufficient to evaluate a drug-associated risk for major birth defects or miscarriage. Based on animal studies, RINVOQ/RINVOQ LQ has the potential to adversely affect a developing fetus. Advise patients of reproductive potential and pregnant patients of the potential risk to the fetus.

In animal embryo-fetal development studies, oral upadacitinib administration to pregnant rats and rabbits at exposures equal to or greater than approximately 1.6 and 15 times the 15 mg tablet dose, 0.8 and 7.6 times the 30 mg tablet dose, and 0.6 and 5.6 times the maximum recommended human dose (MRHD) of 45 mg (on an AUC basis) resulted in dose-related increases in skeletal malformations (rats only), an increased incidence of cardiovascular malformations (rabbits only), increased post-implantation loss (rabbits only), and decreased fetal body weights in both rats and rabbits. No developmental toxicity was observed in pregnant rats and rabbits treated with oral upadacitinib during organogenesis at exposures approximately 0.29 and 2.2 times the 15 mg dose, 0.15 times and 1.1 times the 30 mg dose, and at 0.11 and 0.82 times the MRHD (on an AUC basis). In a pre- and post-natal development study in pregnant female rats, oral upadacitinib administration at exposures approximately 3 times the 15 mg dose, 1.4 times the 30 mg dose, and the same as the MRHD (on an AUC basis) resulted in no maternal or developmental toxicity (*see Data).*

The background risks of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriages are 2-4% and 15-20%, respectively.

Clinical Considerations

*Disease-Associated Maternal and/or Embryo/Fetal Risk*

Published data suggest that increased disease activity is associated with the risk of developing adverse pregnancy outcomes in women with rheumatoid arthritis or inflammatory bowel disease. Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

Data

*Animal Data*

In an oral embryo-fetal development study, pregnant rats received upadacitinib at doses of 5, 25, and 75 mg/kg/day during the period of organogenesis from gestation day 6 to 17. Upadacitinib was teratogenic (skeletal malformations that consisted of misshapen humerus and bent scapula) at exposures equal to or greater than approximately 1.7 times the 15 mg tablet dose, 0.9 times the 30 mg tablet dose, and 0.6 times the MRHD (on an AUC basis at maternal oral doses of 5 mg/kg/day and higher). Additional skeletal malformations (bent forelimbs/hindlimbs and rib/vertebral defects) and decreased fetal body weights were observed in the absence of maternal toxicity at an exposure approximately 84 times the 15 mg dose, 43 times the 30 mg dose, and 31 times the MRHD (on an AUC basis at a maternal oral dose of 75 mg/kg/day).

In a second oral embryo-fetal development study, pregnant rats received upadacitinib at doses of 1.5 and 4 mg/kg/day during the period of organogenesis from gestation day 6 to 17. Upadacitinib was teratogenic (skeletal malformations that included bent humerus and scapula) at exposures approximately 1.6 times the 15 mg dose, 0.8 times the 30 mg dose, and 0.6 times the MRHD (on an AUC basis at maternal oral doses of 4 mg/kg/day). No developmental toxicity was observed in rats at an exposure approximately 0.29 times the 15 mg tablet dose, 0.15 times the 30 mg tablet dose, and 0.11 times the MRHD (on an AUC basis at a maternal oral dose of 1.5 mg/kg/day).

In an oral embryo-fetal developmental study, pregnant rabbits received upadacitinib at doses of 2.5, 10, and 25 mg/kg/day during the period of organogenesis from gestation day 7 to 19. Embryolethality, decreased fetal body weights, and cardiovascular malformations were observed in the presence of maternal toxicity at an exposure approximately 15 times the 15 mg tablet dose, 7.6 times the 30 mg tablet dose, and 5.6 times the MRHD (on an AUC basis at a maternal oral dose of 25 mg/kg/day). Embryolethality consisted of increased post-implantation loss that was due to elevated incidences of both total and early resorptions. No developmental toxicity was observed in rabbits at an exposure approximately 2.2 times the 15 mg tablet dose, 1.1 times the 30 mg tablet dose, and 0.82 times the MRHD (on an AUC basis at a maternal oral dose of 10 mg/kg/day).

In an oral pre- and post-natal development study, pregnant female rats received upadacitinib at doses of 2.5, 5, and 10 mg/kg/day from gestation day 6 through lactation day 20. No maternal or developmental toxicity was observed in either mothers or offspring, respectively, at an exposure approximately 3 times the 15 mg tablet dose, 1.4 times the 30 mg tablet dose, and at approximately the same exposure as the MRHD (on an AUC basis at a maternal oral dose of 10 mg/kg/day).

**Lactation**

Risk Summary

There are no data on the presence of upadacitinib in human milk, the effects on the breastfed infant, or the effects on milk production. Available pharmacodynamic/toxicological data in animals have shown excretion of upadacitinib in milk *(see Data).* When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of the potential for serious adverse reactions in the breastfed infant, advise patients that breastfeeding is not recommended during treatment with RINVOQ/RINVOQ LQ, and for 6 days (approximately 10 half-lives) after the last dose.

Data

A single oral dose of 10 mg/kg radiolabeled upadacitinib was administered to lactating female Sprague-Dawley rats on post-partum days 7-8. Drug exposure was approximately 30-fold greater in milk than in maternal plasma based on $AUC_{0-t}$ values. Approximately 97% of drug-related material in milk was parent drug.

**Females and Males of Reproductive Potential**

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to starting treatment with RINVOQ/RINVOQ LQ *[see Use in Specific Populations].*

Contraception

*Females*

Based on animal studies, upadacitinib may cause embryo-fetal harm when administered to pregnant women *[see Use in Specific Populations].* Advise female patients of reproductive potential to use effective contraception during treatment with RINVOQ/RINVOQ LQ and for 4 weeks after the final dose.

**Pediatric Use**

Ankylosing Spondylitis, Non-radiographic Axial Spondyloarthritis, Ulcerative Colitis, and Crohn's Disease

The safety and effectiveness of RINVOQ/RINVOQ LQ in pediatric patients with ankylosing spondylitis, non-radiographic axial spondyloarthritis, ulcerative colitis, or Crohn's disease have not been established.

**Geriatric Use**

Ulcerative Colitis

Of the 1097 patients treated in the controlled clinical trials, a total of 95 patients with ulcerative colitis were 65 years and older. Clinical studies of RINVOQ did not include sufficient numbers of patients 65 years of age and older with ulcerative colitis to determine whether they respond differently from younger adult patients.

Crohn's Disease

Of the 1021 patients who were treated in the controlled induction clinical trials, a total of 39 patients with Crohn's disease were 65 years of age or older, and no patients were 75 years of age or older. Clinical studies of RINVOQ did not include sufficient numbers of patients 65 years of age and older with Crohn's disease to determine whether they respond differently from younger adult patients.

**Renal Impairment**

For patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, pJIA, or giant cell arteritis no dosage adjustment is needed in patients with mild (eGFR 60 to < 90 mL/min/1.73 m$^2$), moderate (eGFR 30 to < 60 mL/min/1.73 m$^2$), or severe renal impairment (eGFR 15 to < 30 mL/min/1.73 m$^2$).

For patients with atopic dermatitis, the maximum recommended dosage of RINVOQ is 15 mg once daily for patients with severe renal impairment. No dosage adjustment is needed in patients with mild or moderate renal impairment.

For patients with ulcerative colitis or Crohn's disease, the recommended dosage of RINVOQ for severe renal impairment is 30 mg once daily for induction and 15 mg once daily for maintenance. No dosage adjustment is needed in patients with mild or moderate renal impairment.

RINVOQ/RINVOQ LQ has not been studied in patients with end stage renal disease (eGFR <15 mL/min/1.73m$^2$). Use in patients with atopic dermatitis, ulcerative colitis, or Crohn's disease with end stage renal disease is not recommended.

**Hepatic Impairment**

The use of RINVOQ/RINVOQ LQ has not been studied in patients with severe hepatic impairment (Child Pugh C), and is therefore not recommended.

For patients with rheumatoid arthritis, psoriatic arthritis, atopic dermatitis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, pJIA, or giant cell arteritis, no dosage adjustment is needed in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment.

For patients with ulcerative colitis or Crohn's disease, the recommended dosage of RINVOQ for mild to moderate hepatic impairment is 30 mg once daily for induction and 15 mg once daily for maintenance.

## CLINICAL PHARMACOLOGY

**Pharmacokinetics**

RINVOQ tablets and RINVOQ LQ are not bioequivalent; therefore, the 2 dosage forms are not interchangeable on a milligram-per-milligram basis.

## NONCLINICAL TOXICOLOGY

### Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

The carcinogenic potential of upadacitinib was evaluated in Sprague-Dawley rats and Tg.rasH2 mice. No evidence of tumorigenicity was observed in male or female rats that received upadacitinib for up to 101 weeks at oral doses up to 15 or 20 mg/kg/day, respectively (approximately 4 and 10 times the 15 mg tablet dose, 2 and 5 times the 30 mg tablet dose, and 1.6 and 4 times the maximum recommended human dose (MRHD) of 45 mg on an AUC basis, respectively). No evidence of tumorigenicity was observed in male or female Tg.rasH2 mice that received upadacitinib for 26 weeks at oral doses up to 20 mg/kg/day.

Mutagenesis

Upadacitinib tested negative in the following genotoxicity assays: the *in vitro* bacterial mutagenicity assay (Ames assay), *in vitro* chromosome aberration assay in human peripheral blood lymphocytes, and *in vivo* rat bone marrow micronucleus assay.

Impairment of Fertility

Upadacitinib had no effect on fertility in male or female rats at oral doses up to 50 mg/kg/day in males and 75 mg/kg/day in females (approximately 42 and 84 times the 15 mg dose, 22 and 43 times the 30 mg dose, and 16 and 31 times the MRHD, respectively, on an AUC basis). However, maintenance of pregnancy was adversely affected at oral doses of 25 mg/kg/day and 75 mg/kg/day based upon dose-related findings of increased post-implantation losses (increased resorptions) and decreased numbers of mean viable embryos per litter (approximately 22 and 84 times the 15 mg tablet dose, 11 and 43 times the 30 mg tablet dose, and 8 and 31 times the MRHD on an AUC basis, respectively). The number of viable embryos was unaffected in female rats that received upadacitinib at an oral dose of 5 mg/kg/day and were mated to males that received the same dose (approximately 2 times the 15 mg dose, 0.9 times the 30 mg dose, and at 0.6 times the MRHD on an AUC basis).

## PATIENT COUNSELING INFORMATION

Advise the patient and caregiver to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Serious Infections

Inform patients that they may be more likely to develop infections when taking RINVOQ/RINVOQ LQ. Instruct patients to contact their healthcare provider immediately during treatment if they develop any signs or symptoms of an infection *[see Warnings and Precautions]*.

Advise patients that the risk of herpes zoster is increased in patients taking RINVOQ/RINVOQ LQ and in some cases can be serious *[see Warnings and Precautions]*.

Malignancies

Inform patients that RINVOQ/RINVOQ LQ may increase their risk of certain cancers and that periodic skin examinations should be performed while using RINVOQ/RINVOQ LQ.

Advise patients that exposure to sunlight and UV light should be limited by wearing protective clothing and using a broad-spectrum sunscreen *[see Warnings and Precautions]*.

Major Adverse Cardiovascular Events

Inform patients that RINVOQ/RINVOQ LQ may increase their risk of major adverse cardiovascular events (MACE) including myocardial infarction, stroke, and cardiovascular death. Instruct all patients, especially current or past smokers or patients with other cardiovascular risk factors, to be alert for the development of signs and symptoms of cardiovascular events *[see Warnings and Precautions]*.

Thrombosis

Inform patients that events of deep venous thrombosis and pulmonary embolism have been reported in clinical trials with RINVOQ. Instruct patients to seek immediate medical attention if they develop any signs or symptoms of a DVT or PE *[see Warnings and Precautions]*.

Hypersensitivity Reactions

Advise patients to discontinue RINVOQ/RINVOQ LQ and seek immediate medical attention if they develop any signs and symptoms of allergic reactions *[see Warnings and Precautions]*.

Gastrointestinal Perforations

Inform patients that gastrointestinal perforations have been reported in clinical trials with RINVOQ and that risk factors include the use of NSAIDs, corticosteroids, or history of diverticulitis. Instruct patients to seek medical care immediately if they experience new onset of abdominal pain, fever, chills, nausea, or vomiting *[see Warnings and Precautions]*.

Retinal Detachment

Inform patients that retinal detachment has been reported in clinical trials with RINVOQ. Advise patients to immediately inform their healthcare provider if they develop any sudden changes in vision while receiving RINVOQ/RINVOQ LQ *[see Adverse Reactions]*.

Laboratory Abnormalities

Inform patients that RINVOQ/RINVOQ LQ may affect certain lab tests, and that blood tests are required before and during RINVOQ/RINVOQ LQ treatment *[see Warnings and Precautions]*.

Vaccinations

Advise patients to avoid use of live vaccines with RINVOQ/RINVOQ LQ. Instruct patients to inform their healthcare practitioner that they are taking RINVOQ/RINVOQ LQ prior to a potential vaccination *[see Warnings and Precautions]*.

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential that exposure to RINVOQ/RINVOQ LQ during pregnancy may result in fetal harm. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions and Use in Specific Populations]*.

Advise females of reproductive potential that effective contraception should be used during treatment and for 4 weeks following the final dose of RINVOQ/RINVOQ LQ *[see Use in Specific Populations]*.

Advise women exposed to RINVOQ/RINVOQ LQ during pregnancy that there is a pregnancy surveillance program that monitors pregnancy outcomes *[see Use in Specific Populations]*.

Lactation

Advise women not to breastfeed during treatment with RINVOQ/RINVOQ LQ and for 6 days after the last dose *[see Use in Specific Populations]*.

Administration

Advise patients that RINVOQ tablets are not substitutable with RINVOQ LQ.

Advise patients not to chew, crush, or split RINVOQ tablets.

For RINVOQ LQ, instruct patients and caregivers to read and follow the Instructions for Use for proper preparation, administration, storage, and disposal.

Advise patients to avoid food or drink containing grapefruit during treatment with RINVOQ/RINVOQ LQ *[see Drug Interactions]*.

Medication Residue in Stool

Instruct patients to notify their healthcare provider if they repeatedly notice medication residue (e.g., intact RINVOQ tablet or fragments) in stool or ostomy output *[see Warnings and Precautions]*.

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LAB-13658 **MASTER**

US-RNQG-260002

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# Inflammatory bowel disease: A century of change

A look at how far IBD care has come — from early debates and limited therapies to patient-centered strategies, new tools, and emerging insights that are shaping the future of treatment.

In honor of World IBD Day this month (May 19), in this issue we highlight several articles demonstrating how far we have come in the management of inflammatory bowel disease.

My gastroenterology fellowship training occurred in a time when biologics had not yet been approved for treatment of IBD. We rarely saw patients from Africa, Asia, or Latin America with IBD. We told our patients to eat whatever felt good. We measured success on clinical improvement. At meetings we had discussions about "top down" or "bottom up" treatment strategies. How times have changed!

In my 25 years in private practice, the advancements made in IBD therapy have been life-changing for patients living with Crohn's disease and ulcerative colitis. We have moved from bench research to the development of highly effective therapies to treat IBD. In this century, we recognize that IBD can occur in any part of the world and can affect people across diverse populations. We have accepted the importance of a "healthy diet" and encourage patients to eat more fruits and vegetables. We have learned to listen and partner with our patients to create treatment plans that recognize the patient's preferences, values, and beliefs. IBD therapy has moved from a disease-centered approach to a patient-centered approach. We have discussions about "treat to target." These are exciting times in the IBD world.

In this month's issue, we summarize AGA's new IBD Drug Guide, a web-based tool that allows the patient and the provider to take a short quiz, rank treatment preferences, and have a discussion regarding medical options that align with the patient's priorities. This is a free, easy to use tool for the busy clinician and should facilitate a healthy discussion. We share a report from researchers showing a potential difference in post operative Crohn's recurrence in men and women using molecular biomarkers. Men and women are different in many ways including the rates of post-operative disease recurrence. Finally, the Capsule & Omics for Predicting Exacerbation of Crohn's disease (CORE-CD) indicates a link between unhealthy eating patterns and impairment of "gut barrier homeostasis."

We also highlight MASLD updates, including the new AGA MASLD clinical care pathway that offers a more streamlined approach to screening, risk stratification, and treatment. Finally, we share an article showing an increased risk of HCC in MASLD patients with advanced fibrosis or cirrhosis.

Kimberly M. Persley, MD, AGAF
Associate Editor

## Supporting the AGA Research Foundation is a return on investment

Decades of research have revolutionized the care of many digestive disease patients. These patients, as well as everyone in the GI field — clinicians and researchers alike, have benefited from the discoveries of dedicated investigators, past and present. Right now, creative young researchers are poised to make groundbreaking discoveries that will shape the future of gastroenterology. Unfortunately, declining government funding for biomedical research puts this potential in jeopardy. We're at risk of losing an entire generation of researchers.

To fill this gap, the AGA Research Foundation invites you to support young investigators' research careers. Your gift will allow them to make discoveries that could ultimately improve patient care and even cure diseases.

"The future of our field depends on advances made in research, both bench and clinical. I see firsthand that it's increasingly difficult for investigators to secure funding, particularly those in the early stages of their career. We can't afford to have our pipeline of researchers dry up. The AGA Research Foundation provides the funds that are necessary for these young investigators to continue their work and contribute to the field. That's why I support the foundation," said Mark Donowitz, MD, AGA Legacy Society member.

By joining others in supporting the AGA Research Foundation, you will ensure that young researchers have opportunities to continue their life-saving work. Learn more or make a contribution at foundation.gastro.org.

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**Director of Business Development – Advertising Sales** Wynn Hansen
**Contact Information** +1 813-797-6033 wynn.hansen@conexiant.com

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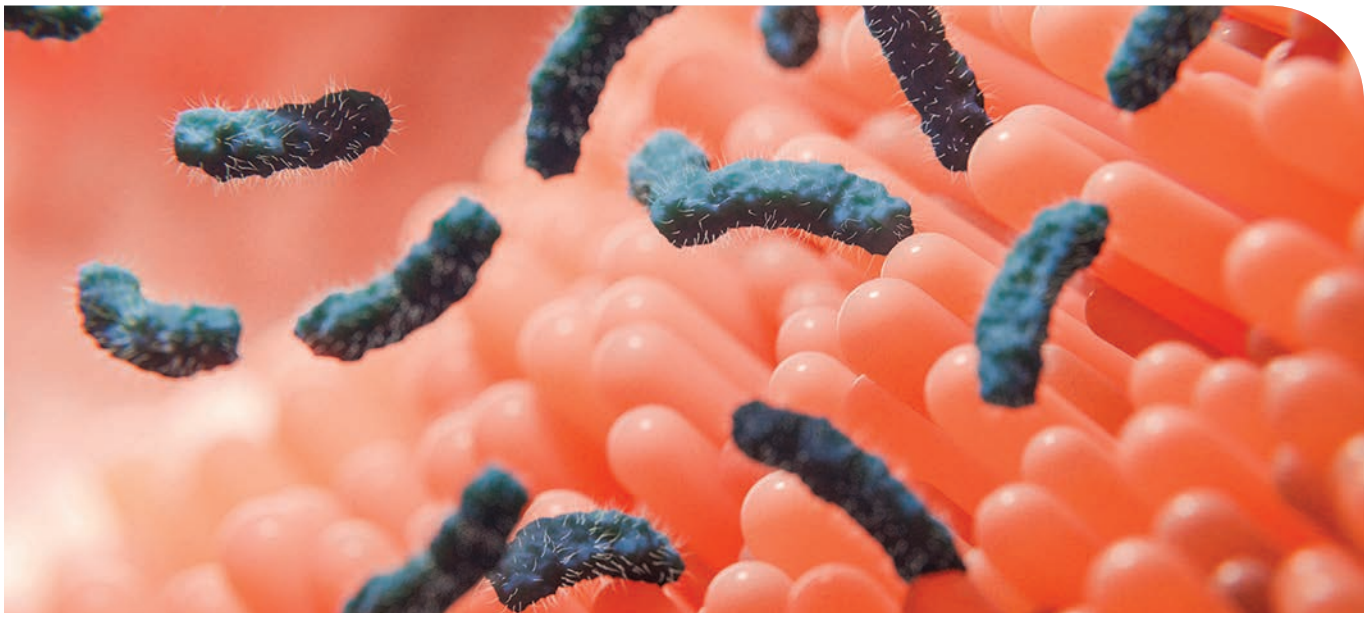
*Linerixibat "is an added therapy that's mechanistically different from what we have; and therefore I think that it's going to be used."*

Don C. Rockey, MD • See Page 17

# AGA launches patient-focused IBD Drug Guide

The tool evaluates therapies based on three key factors: safety, efficacy, and convenience.

By Doug Brunk



Credit: Adobestock.com

Joseph D. Feuerstein, MD

AGA has introduced a free, web-based IBD Drug Guide designed to help patients and clinicians navigate the increasingly complex landscape of inflammatory bowel disease (IBD) treatment.

Historically, treatment strategies for Crohn's disease and ulcerative colitis followed straightforward "step-up" or "top-down" approaches. Today, however, clinicians must weigh a broader range of biologics and small molecules, along with payer preferences and patient priorities.

While clinicians, insurers, and patients may each have their own preferences, optimal IBD care should center on a collaborative approach, noted Joseph D. Feuerstein, MD, Clinical Chief of Gastroenterology at Beth Israel Deaconess Medical Center and Associate Professor of Medicine at Harvard Medical School, Boston, who chaired the effort to assemble the guide.

"What this should come down to is shared decision-making about what is the best drug for the patient," he told *GI & Hepatology News*. Despite this need, he added, there has been no comprehensive, patient-friendly tool to guide those discussions. This prompted AGA to convene a multidisciplinary team of gastroenterologists, pharmacists, psychologists, and patients to develop the new resource.

## Three core pillars

At the heart of the IBD Drug Guide is a structured framework that evaluates therapies based on three key factors: safety, efficacy, and convenience. Users complete a brief, two-minute quiz that captures disease severity, treatment goals, and personal preferences. The tool then ranks therapies, helping patients and clinicians compare trade-offs and identify best options.

"Everyone weighs those three pillars in different ways," Dr. Feuerstein explained. "That's really what is important as to how we think about this."

The development process involved independent scoring of therapies by experts, followed by group review to reach consensus, an approach that yielded strong agreement across the panel.

## Enhancing conversations in the clinic

The guide is designed for flexibility, allowing patients to use it before appointments or to complete it alongside their clinician during office visits. Dr. Feuerstein said he has already incorporated it into his own practice. In one example, a patient with severe disease might clinically benefit most from a highly effective biologic such as infliximab. However, if that patient prioritizes safety over efficacy, the tool may instead highlight alternatives with more favorable safety profiles.

"What's remarkable is I actually find that it really always comes up with the top three drugs that I was thinking of anyway," Dr. Feuerstein said, noting that the tool reinforces and clarifies clinical judgment while engaging patients in the process.

## A living resource

The IBD Drug Guide officially launched in November 2025 and is intended to evolve alongside the field. "We're going to work with AGA to continue to update it on a routine basis as new drugs come to market," he said.

*The initiative is supported by independent educational grants from AbbVie and Bristol Myers Squibb.*

*Scan the QR code to access the IBD Drug Guide.*

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# Five startups reach AGA Shark Tank finals

"It's more about the inspiration than about the winner."

By Doug Brunk

Eric Shah, MD, MBA

For many physicians, today's health care environment can feel increasingly out of their control. But Eric Shah, MD, MBA, sees something else emerging: a chance to redefine the profession and reclaim its sense of purpose.

That spirit was on full display at AGA's Shark Tank Pitch competition on the first day of the 2026 AGA Tech Summit in Chicago on April 9. Five early-stage companies were selected as finalists. They presented new ideas for improving gastrointestinal care, including endoscopic tools and AI-based platforms. Edulis Therapeutics was named the winner.

"This is a challenging time for the profession," Dr. Shah, the Tech Summit's program chair, told *GI & Hepatology News*, pointing to a health care system increasingly shaped by consolidation, one that can leave both patients and physicians feeling like "widgets." But rather than seeing this as decline, he views it as a turning point, an opportunity for physicians to rethink what health care could become.

The Shark Tank competition, he explained, isn't about spotlighting flashy personalities or creating the next social media star. It's about something quieter and arguably more powerful. "We're after the people that really want to make a difference," said Dr. Shah, Associate Professor in the Division of Gastroenterology and Hepatology at the University of Michigan in Ann Arbor.

Each finalist is tackling a different challenge in GI and hepatology, highlighting the growing overlap between medical technology, drug delivery, and digital health. A panel of judges chose the winner based on clinical impact, market potential, and readiness for adoption.

## Long-acting drug delivery for Crohn's disease

The winner, Edulis Therapeutics, is focused on improving treatment for Crohn's disease, particularly stricturing disease. The company has developed an endoscopic drug-delivery system that implants medication directly into the gastrointestinal tract during a routine exam.

The implant is designed to release medication over as long as 12 months, potentially reducing the need for repeated infusions or procedures. Current Crohn's treatments can be costly and burdensome, and many patients still require surgery.

Edulis is pursuing a combination regulatory pathway that would allow approval of both its delivery device and drug implant. The company believes its platform could extend the effectiveness of existing therapies and improve safety by localizing treatment within the GI tract.

## A sprayable solution for GI bleeding

BioDevek is developing a sprayable endoscopic device designed to control gastrointestinal bleeding and protect injured tissue. The single-use system combines polymer components delivered through an endoscope, allowing physicians to treat bleeding lesions during procedures.

The company is initially targeting non-variceal upper GI bleeding, a common and sometimes difficult-to-control condition. Its approach aims not only to stop bleeding but also to create a protective barrier over the affected area, potentially reducing rebleeding and complications.

BioDevek plans to pursue FDA clearance through the 510(k) pathway and expects adoption among hospitals and ambulatory endoscopy centers. The company also sees broader applications for its material platform, including post-procedure tissue protection and drug delivery at the site of injury.

## Advanced imaging for cancer surveillance

Lumicell is targeting earlier and more accurate detection of esophageal and gastric cancers. Its imaging platform is designed for use in high-risk surveillance populations, such as patients with Barrett's esophagus or gastric intestinal metaplasia.

These conditions require regular monitoring, but current approaches can miss early changes. Lumicell's technology aims to enhance visualization during endoscopy, helping clinicians identify suspicious tissue more reliably.

The company estimates a large and growing market, with more than 1.6 million relevant surveillance procedures performed annually in the US.


Spencer Matonis, PhD: Edulis Therapeutics Founder and CEO
Juan Genere, MD: Clinical Partner

*"This isn't the decline of medicine — it's a turning point, a chance for physicians to redefine their profession and reclaim its purpose."*

## AI tools to reduce denied claims

Protego Health is taking a different angle on GI care, focusing on the financial and administrative challenges providers face. According to the company's executive summary, its platform uses artificial intelligence to validate claims, identify potential denials before submission, and generate appeals.

The system integrates with electronic health records and uses coding rules and payer-specific policies to flag issues in real time. By preventing denials and streamlining appeals, Protego aims to improve revenue cycle management for health care organizations.

While not a clinical tool, the platform addresses a key pain point in GI practices, where reimbursement complexity can affect access to care.

## A 'diagnostic-first' platform for GI care navigation

Second Brain Healthcare is developing a digital platform designed to improve how patients with digestive symptoms are diagnosed and treated. The company describes GI care as inefficient, with long wait times, unnecessary referrals, and frequent diagnostic delays.

Its solution uses structured intake and a diagnostic engine to identify likely causes of symptoms and guide patients to appropriate care. The platform also adapts treatment over time, aiming to reduce unnecessary procedures and lower costs.

In early validation studies, the system achieved more than 90% agreement with specialist diagnoses and reduced unnecessary referrals and testing.

Second Brain is initially targeting employers and health plans, positioning its technology as a way to improve outcomes while reducing spending in a high-cost area of health care.

## A snapshot of GI innovation

For Tech Summit attendees, the value of the Shark Tank competition goes far beyond who wins, Dr. Shah said. Each pitch offered a different lens on how innovation can take shape. Different styles, different strategies, different stages — all unfolding in a way that feels less like a competition and more like a learning experience.

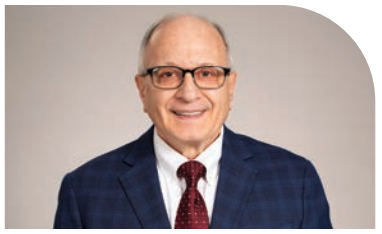
"It's more about the inspiration than about the winner," he said.

Dr. Shah also believes future contestants will be sitting in the audience at this year's meeting.

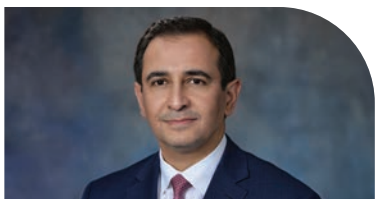
"Some of the registrants now will be Shark Tank finalists in five years," he said. "But getting there doesn't start with having a perfect idea; it starts with showing up. The five-year clock doesn't start until the day you register to attend."

# AGA unveils its annual recognition award winners

Awardees to be honored at Digestive Disease Week® (DDW) 2026.



*Award:* William Beaumont Prize in Gastroenterology
*Recipient:* Stuart Jon Spechler, MD, AGAF, MACG, FAFS
*Title:* Chief, Division of Gastroenterology, Baylor University Medical Center
*Testimonial:* "I am so thrilled to be the 2026 recipient of the William Beaumont Prize in Gastroenterology. In my clinical and translational research, my goal has always been to advance the care of patients with digestive diseases. I am incredibly honored to be recognized by AGA with this prize for my contributions in that regard."



*Award:* Julius Friedenwald Medal
*Recipient:* Hashem El-Serag, MD, MPH
*Title:* Vice President, Learning Health System, Margaret M. and Albert B. Alkek Professor and Chair, Department of Medicine, Baylor College of Medicine
*Testimonial:* "I am deeply honored to receive the Julius Friedenwald Medal from AGA. I accept it with deep gratitude on behalf of the mentors, colleagues, trainees, and collaborators whose partnership has made our collective work to advance gastroenterology and hepatology possible."

*Award:* Distinguished Clinician Award, Private Practice
*Recipient:* Jeffry Nestler, MD
*Title:* President of Connecticut GI, PC/ Co-Physician-in-Chief of the Hartford HealthCare Digestive Health Institute, Hartford Healthcare
*Testimonial:* "It is a tremendous honor to receive this award which is deeply meaningful to me. It reflects the privilege I have had to work alongside extraordinary colleagues, mentors, and teams who are all committed to advancing patient care and our profession. I am grateful for the opportunity to contribute to a field and community that has given me so much over the course of my career."

*Award:* Distinguished Service Award in Diversity, Equity and Inclusion
*Recipient:* Rachel Issaka, MD, MAS
*Title:* Associate Professor; Director, Population Health Colorectal Cancer Screening Program; Kathryn Surace-Smith Endowed Chair in Health Equity Research, Fred Hutch Cancer Center, Seattle
*Testimonial:* "Receiving the AGA Diversity, Equity and Inclusion Award is a profound validation of our shared commitment to addressing inequities in gastrointestinal health."

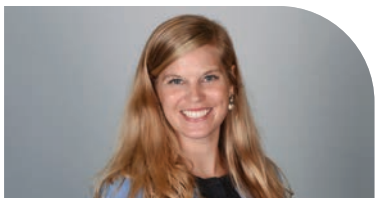
*Award:* Distinguished Mentor Award
*Recipient:* Nicholas Davidson, MD, DSc
*Title:* John E. and Adaline Simon Professor of Medicine and Developmental Biology; Director, Digestive Disease Research Core Center; Chief, Division of Gastroenterology, WashU Medicine
*Testimonial:* "I am deeply honored to be recognized with the AGA Distinguished Mentor Award, as a reflection of my lifelong commitment to nurturing and supporting future generations of leaders in gastroenterology. This award also celebrates the accomplishments and goals of my mentees and validates our collective mission in fostering an environment that advances patient care and discovery, while developing and nurturing the next generation of leaders."

*Award:* Distinguished Clinician Award, Academic Practice
*Recipient:* William M. Lee, MD
*Title:* Professor Emeritus of Internal Medicine, University of Texas Southwestern Medical Center at Dallas
*Testimonial:* "It is a great personal honor to have been nominated for and to have received this amazing award. I couldn't imagine a more fulfilling, gratifying, or fun career, which must be why I continued on until age 84! I would like to thank the many colleagues, patients and staff who supported me so loyally over these many years."

*Award:* Distinguished Educator Award
*Recipient:* Steven Itzkowitz, MD, FACP, FACG, AGAF
*Title:* Professor of Medicine, Oncological Sciences and Medical Education, Icahn School of Medicine at Mount Sinai
*Testimonial:* "Being an educator is an integral part of my identity. I am a firm believer in the adage: 'Give a person a fish, and you feed them for a day; teach a person to fish, and you feed them for a lifetime.' While I have been recognized for lifelong service as a medical educator by my home institution, and a national Gold Humanism award, receiving the 2026 Distinguished Educator Award from AGA fills me with enormous pride that my efforts are appreciated at the national level. I am completely indebted to my mentors, my students, my trainees and mentees, my patients, and most importantly, my family — all of whom taught me the wisdom and lessons I try my best to convey to others."

*Award:* Distinguished Achievement Award in Basic Science
*Recipient:* Klaus H. Kaestner, PhD, MS
*Title:* Suor Butterworth Professor of Genetics, University of Pennsylvania Perelman School of Medicine
*Testimonial:* "Having the work of my laboratory over the last three decades validated by AGA Distinguished Achievement Award in Basic Science means the world to me. It is wonderful to realize that my esteemed colleagues value my contributions."

*Award:* Young Investigator Award in Clinical Science
*Recipient:* Manasi Agrawal, MD, MS
*Title:* Assistant Professor of Medicine/Director of Environmental Gastroenterology, Icahn School of Medicine at Mount Sinai
*Testimonial:* "Receiving the AGA Young Investigator Award is a highly meaningful recognition from one of the most respected societies in our field, affirming the impact of early-career research to gastroenterology. For me, it represents an encouragement to continue pursuing rigorous, high-impact questions at the intersection of environmental health and inflammatory bowel disease."



*Award:* Young Investigator Award in Basic Science
*Recipient:* Melinda Engevik, PhD
*Title:* Associate Professor, Medical University of South Carolina
*Testimonial:* "Receiving the AGA Young Investigator Award in Basic Science is a tremendous honor, and I am sincerely grateful to the AGA community for their support throughout my career. This recognition reflects the dedication, creativity, and hard work of my trainees and collaborators, whose contributions make these discoveries possible. It also underscores the importance of fundamental research in advancing our understanding of gastrointestinal biology and disease. I am deeply appreciative of AGA for fostering a collaborative and innovative scientific community, and I am honored to be part of it."

# Gut abnormalities persist even in Crohn's remission

Multi-omics analysis reveals ongoing epithelial and microbial disruption despite effective immune suppression.

By Doug Brunk

Patients with Crohn's disease (CD) in corticosteroid-free clinical remission still show abnormalities in the gut lining, microbiome, metabolism, and diet, despite strong suppression of mucosal immune pathways, according to a multi-omics analysis published in *Gastroenterology*.

"The remitting-relapsing nature of CD is likely driven by the fact that current advanced therapies only address one side of the disease: the immune response," the study's corresponding author, Yael Haberman, MD, PhD, a pediatric gastroenterologist at Sheba Medical Center, Tel HaShomer, Israel, and an adjunct faculty member at the Cincinnati Children's Hospital Medical Center, told *GI & Hepatology News*. "The underlying perturbations in diet, the microbiome, metabolites, and epithelial barrier function remain largely untouched. To achieve a 'deeper, longer-lasting remission,' it may be necessary to broaden the therapeutic focus to include restoring the gut's physical and metabolic health through targeted dietary, microbiome, and epithelial interventions."

Crohn's disease therapies have increasingly focused on immune suppression but less is known about how other components of gut biology behave during clinical remission.

In an analysis of 191 subjects recruited for a study known as Capsule & Omics for Predicting Exacerbation of Crohn's disease (CORE-CD), investigators compared 77 patients with CD in stable remission, 37 patients with active, mostly treatment-naïve CD, and 77 non-IBD controls. Although immune-related gene expression in the ileum was significantly reduced during remission, often to levels lower than those observed in controls, markers of epithelial antimicrobial activity and mucus biology remained elevated. These transcriptomic findings were accompanied by persistent dysbiosis, changes in fecal metabolism, and dietary patterns characterized by higher consumption of ultra-processed foods and lower intake of fiber and micronutrients.

Patients in remission had been clinically stable for at least three months with a Crohn's Disease Activity Index below 150 and stable medication dosing; most were receiving biologic therapy. Inflammatory markers such as C-reactive protein were comparable to controls and significantly lower than in active CD. Fecal calprotectin levels were reduced relative to active disease but not fully normalized in all patients. A subset undergoing video capsule endoscopy demonstrated small bowel inflammatory scores, some with levels previously associated with increased flare risk.

RNA sequencing of tissue from the ileum showed that, during remission, genes related to adaptive T cells and innate granulocyte pathways were broadly reduced compared with controls, suggesting that immune activity had dropped below normal levels. However, the antimicrobial response in the epithelial cells remained active. Genes including DUOX2, CEACAM6, and REG1B were persistently upregulated during remission, approaching levels seen in active disease. Functional enrichment analysis confirmed sustained activation of antibacterial pathways.

At the same time, genes associated with goblet cells and mucin glycosylation were significantly induced in remission compared with both controls and active CD. Summary of co-expressed gene signals eigengene analysis showed that mucin-related pathways were selectively increased during remission. When the researchers stratified patients by six-month outcomes, they found that those who later had a flare already showed higher levels of genes related to the gut lining's antimicrobial defenses and mucus production at the start of the study. In contrast, differences in adaptive immune suppression did not help predict who would flare and who would stay in remission.

Analysis of stool samples showed that even when patients were in remission, their gut bacteria had not returned to a healthy balance. Compared with controls, patients in remission had a higher IBD dysbiosis index, lower microbial diversity, and persistent enrichment of taxa previously linked to CD, including *Escherichia*, *Ruminococcus gnavus*, and *Enterocloster bolteae*. Fecal metabolomics demonstrated that most metabolites altered in remission relative to controls were perturbed in the same direction as in active CD, indicating durable metabolic disruption despite clinical quiescence.

Dietary assessment using a validated food frequency questionnaire revealed that patients with CD, regardless of disease activity, consumed more ultra-processed foods and added sugars and fewer vegetables, fiber, folate, and vitamins C and K compared with controls. Principal component analysis demonstrated clear separation between CD and control dietary patterns. Higher exposure to ultra-processed foods correlated with greater microbial dysbiosis, whereas higher intake of olive oil, vegetables, and certain micronutrients was associated with more favorable microbial indices.

Importantly, ultra-processed food exposure was negatively correlated with mucin glycosylation gene signatures, while adherence to a Mediterranean-style diet was positively associated with these epithelial pathways. Neither fecal calprotectin nor the microbial dysbiosis index significantly correlated with mucin-related gene expression.

An outside expert said the findings highlight the complexity of Crohn's disease even during apparent clinical remission.

Ruben Colman, MD, PhD

"This study helps explain why patients with Crohn's disease frequently experience disease exacerbations," said Ruben Colman, MD, PhD, director of intestinal ultrasound at Stanford University's Center for IBD and Celiac Disease in Palo Alto, California. "Using a multiomics approach incorporating gene expression, microbial, metabolomic, and dietary signals, the investigators showed that while biologic therapies effectively suppress immune activity in patients in remission, pathogenic microbial signals and epithelial antibacterial signals — including DUOX2 and CEACAM6 — can persist." These findings suggest that achieving deep remission may require adjunctive strategies beyond immune-targeting biologics that address the diet–epithelial–microbial axis, he added.

The authors noted certain limitations of the study, including its cross-sectional design, the absence of interventional dietary data, and the inability to capture medication history beyond biologic exposure and certain lifestyle variables.

*The study was funded by the Helmsley Charitable Trust, the ERC starting grant, the ERC Proof of Concept grant, Israel Science Foundation, Tel Aviv University's Colton Center for Autoimmune Diseases, Israel Science, Culture, and Sport, and Litwin IBD Pioneers Awards. The authors reported having no relevant disclosures.*

*GI & Hepatology News* invited Dr. Haberman to further discuss the implications of the research.

**Why does this study matter?**

**Dr. Haberman:** By comparing patients in remission to those with active disease and healthy controls, the CORE-CD study found that unhealthy eating patterns, specifically the high consumption of ultra-processed foods, persist despite education. These choices are linked to a pathogenic microbial composition and metabolic changes that deviate significantly from a healthy state. Intriguingly, while biologic therapies successfully suppress adaptive immune responses (often below the levels of healthy controls), the gut epithelium remains in a state of high alert, showing elevated antimicrobial signals and a novel increase in goblet cell and mucin glycosylation activity. The study establishes a critical link between ultra-processed food intake and the impairment of mucin glycosylation, a key component of gut barrier homeostasis, suggesting that dietary and epithelial-targeted interventions are necessary adjuncts to current immune-centric treatments.

**When you had all the data in front of you, was there a finding, or more than one, that surprised you?**

**Dr. Haberman:** Ileal transcriptomics revealed that genes associated with adaptive T-cells and innate granulocytes were suppressed in remission patients to levels lower than those observed in non-IBD healthy controls. This highlights the profound impact of advanced biologic therapies on the immune response, yet it stands in stark contrast to the persistent inflammation markers in the epithelium.

Another interesting finding was the induction of genes linked to goblet cells and to mucin glycosylation specifically in patients in remission. In active CD, these signals are typically reduced. The increase during remission may represent a compensatory mechanism to restore the gut barrier or a specific biological signature of a treated state.

Additionally, the study found a clear negative correlation between the consumption of NOVA Class 4 ultra-processed foods and the expression of genes essential for mucin glycosylation. This provides a potential mechanistic explanation for how modern diets are linked with altering the gut barrier's defense systems, independent of the immune system's activity. This contrasted with higher exposure to the Mediterranean diet, which was associated with higher expression of genes essential for mucin glycosylation.

**How might the findings influence clinical practice?**

**Dr. Haberman:** These findings suggest that treating just immune activation may be insufficient for long-term disease clearance. Hence, potential shifts in clinical practice may include three areas of focus:

- **Adjunctive dietary therapy.** Patients and clinicians should focus on reducing ultra-processed food intake, as it is linked to lower expression of mucus barrier genes (mucin glycosylation).
- **Epithelial health monitoring.** Measuring epithelial antimicrobial signals like DUOX2 may provide a more accurate prediction of future flares than traditional immune markers.
- **Targeting the diet-epithelia-microbial axis.** Future management should move beyond simple immune suppression to include strategies that promote a "healthier" CD state through adjunctive dietary modification and metabolite supplementation, along with immune modulation.

# The push to prevent Crohn's disease

Through INTERCEPT, efforts are underway to develop a blood-based risk score capable of predicting CD and to prevent disease onset.

By Doug Brunk

Jean-Frederic Colombel, MD

For more than 40 years, Jean-Frederic Colombel, MD, has cared for patients with inflammatory bowel disease and watched the same pattern repeat itself: months of vague symptoms, delayed referrals, and cycles of steroids. By the time Crohn's disease is firmly diagnosed, irreversible damage has often already occurred.

"What really matters is early," Dr. Colombel, who directs the Susan and Leonard Feinstein Inflammatory Bowel Disease Clinical Center at the Icahn School of Medicine at Mount Sinai, New York, told GI & Hepatology News. "If you are able to catch the disease early, it's a completely different story."

That conviction now underpins one of the most ambitious prevention efforts in gastroenterology: the INTERCEPT study, a sweeping European initiative designed to predict and potentially prevent CD before the first clinical symptom appears.

## A prevention mindset

In the US, as many as half of patients with CD wait up to two years between first symptoms and diagnosis. During that time, inflammation can silently progress. "If you let the disease progress, it's too late," Dr. Colombel said. "The key word is early."

Launched in 2025, INTERCEPT aims to shift the timeline — moving intervention upstream, into the silent biological phase before symptoms begin.

## Mining the preclinical window

The study is supported by the Innovative Health Initiative Joint Undertaking (IHI JU) with Takeda Pharmaceutical Company as the industry lead. It is co-led by Geert D'Haens, MD, PhD, of Stichting Amsterdam University Medical Center and involves multiple partners from several European countries as well as the United States and South Korea. Its first objective is to validate a blood-based risk score capable of identifying people who are likely to develop CD within the next few years.

The blood-based risk score will be directly informed by a blood score being developed in the US and Canada by the PROMISE Consortium (Prediction and Prevention through Omics, Microbiome, Immune System, and Environment). This research group is exploring the predictive and preventative aspects of omics- and microbiome-related, immunological and environmental factors contributing to the development of CD.

Working in this consortium since 2024, Dr. Colombel, along with Icahn School of Medicine colleague Inga Peter, PhD; Dr. Ken Croitoru, MD, of Mount Sinai Hospital in Toronto; and Hamed Khalili, MD, MPH, of Massachusetts General Hospital, have used rare and powerful preclinical cohorts to support their research. One comes from the US Department of Defense serum repository, which stores blood samples from military recruits. Researchers identified 200 individuals who later developed CD, along with 100 matched controls. For each future case, four samples are available: one at diagnosis, and others taken two, four and up to 10 years earlier. The repository offers a unique biological timeline, revealing how immune signals evolve long before symptoms surface.

A second cohort, known as The GEM Project, has followed 5,000 first-degree relatives of CD patients in Canada and other countries for more than a decade. About 150 participants have developed the disease during follow-up, providing another invaluable set of pre-diagnostic samples.

The third resource is the Nurses' Health Study, a long-running study that has collected blood samples from thousands of nurses while tracking a wide range of health outcomes, including IBD.

Together, the cohorts span men and women, younger and older adults, relatives of patients and individuals without known family history. "It's interesting because we can validate our biomarkers across different populations," Dr. Colombel said.

## A 'multi-omics' search

Rather than focusing on a single marker, the research team adopted a broad, multi-omics approach. They analyzed antibodies already associated with CD, scanned more than a thousand circulating proteins, evaluated metabolites and even examined markers of environmental exposure. The process is deliberately expansive and unbiased. But Dr. Colombel expects the final risk score to be practical and streamlined. "What we hope," he said, "is that by measuring just six or

seven biomarkers, you have a very good prediction of the development of Crohn's disease within the next two years."

Importantly, that prediction would apply to individuals who feel well and are asymptomatic for CD.

According to Dr. Colombel, there is a gray zone between truly preclinical disease and silent inflammation. Elevated fecal calprotectin, a stool marker of intestinal inflammation, may signal that microscopic disease has begun and could also help to predict future development of CD. But from a clinical perspective, the distinction matters less than timing. "The most important is to catch the disease before the symptoms," he said.

### From 10,000 to 100

Validation is only the first step. INTERCEPT also includes a massive prospective recruitment effort across seven European countries. The goal: enroll 10,000 first-degree relatives of CD patients and offer them a blood-based risk assessment.

Family history alone increases risk, but not enough to justify preventive therapy. The blood score is designed to refine that risk. Participants with a high-risk profile will undergo stool testing for calprotectin. Those with both a high blood score and elevated stool calprotectin will be eligible for a randomized placebo-controlled prevention trial with vedolizumab.

Because CD remains relatively uncommon — even among relatives — researchers must begin with thousands to identify individuals at sufficiently high risk to test preventive treatment. Recruitment has begun in several countries, though Dr. Colombel describes the cross-border regulatory process as difficult. Still, momentum is building.

### A beginning, not an end

PROMISE and INTERCEPT have been years in the making, and Dr. Colombel is realistic about the timeline. Prevention science moves slowly, requiring careful validation, ethical oversight, and long-term follow-up.

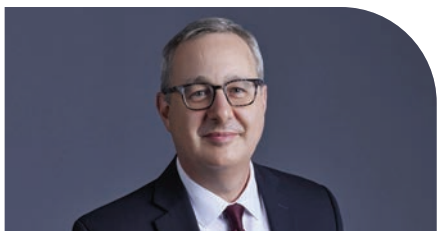
"It will take a long time, but it could transform the care of IBD," he said.

*Dr. Colombel reported having no conflicts of interest.*

# Mirikizumab in Crohn's: Two-year data suggest continued benefit

"There is considerable interest in using these agents earlier in the treatment paradigm."

By Julia Cipriano



Bruce E. Sands, MD, MS

Long-term treatment with mirikizumab, a monoclonal antibody targeting the interleukin-23 p19 subunit (IL-23p19), was associated with sustained improvements across multiple therapeutic targets through two years in patients with moderately to severely active Crohn's disease. Some patients achieved these outcomes during the second year of therapy, according to interim results from the VIVID-2 extension study in press for *Clinical Gastroenterology and Hepatology*.

"These findings suggest that treatment with mirikizumab can offer durable disease control," said lead author Bruce E. Sands, MD, MS, in an interview with *GI & Hepatology News*. "Given the safety of mirikizumab and other anti–IL-23p19 antibodies, there is considerable interest in using these agents earlier in the treatment paradigm."

The results extend findings from the VIVID-1 trial, which demonstrated efficacy and safety through 52 weeks. VIVID-2 reports outcomes after an additional year, representing a total of 104 weeks of continuous therapy. Safety findings during the second year appeared consistent with the known safety profile of mirikizumab.

### A prevention mindset

VIVID-2 enrolled patients who completed VIVID-1. They had moderately to severely active Crohn's disease and had experienced inadequate response, loss of response, or intolerance to conventional or approved biologic therapies.

Among 630 patients who received mirikizumab in VIVID-1 (900 mg intravenously at weeks 0, 4, and 8, followed by 300 mg subcutaneously every 4 weeks through week 52), 572 entered the extension study. A total of 465 patients were included in the safety population and 430 met criteria for the efficacy population, noted Dr. Sands, of the Icahn School of Medicine at Mount Sinai, New York, and colleagues.

Patients who achieved endoscopic response at week 52 of VIVID-1 (n = 251) continued subcutaneous mirikizumab. Those without endoscopic response (n = 179) underwent reinduction with intravenous mirikizumab before returning to maintenance dosing.

### Efficacy

At week 104, endoscopic response was achieved in 60.5% of patients using modified nonresponder imputation (67.1% observed case [OC]), and endoscopic remission occurred in 37.9% (41.7% OC). Clinical remission by Crohn's Disease Activity Index (CDAI) occurred in 73.4% (80.9% OC).

Among patients who had achieved endoscopic response at week 52, most maintained these outcomes through 104 weeks. Endoscopic response was maintained in 81.8% (87.6% OC) of patients, endoscopic remission in 72.5% (78.6% OC), and CDAI remission in 86.9% (92.9% OC). Among week-52 responders who had not yet achieved endoscopic or CDAI remission, 33.3% (35.4% OC) and 55.8% (60.8% OC), respectively, gained those outcomes by week 104.

The corresponding rates of achieving these endpoints were 30.9%, 14.2%, and 65.7% (36.1%, 16.0%, and 75.4% OC), respectively, among week-52 nonresponders.

"Endoscopic healing is a major target that may limit the risk of bowel damage progression and improve long-term outcomes," noted the researchers. Repeat intravenous induction "may be a relevant option in some patients ... thereby avoiding the need to change treatment if endoscopic healing is not achieved."

Nearly all patients who received corticosteroids at baseline (94.3%) were corticosteroid-free at week 104.

### Biomarkers and symptoms

During the first year of VIVID-2, median C-reactive protein (CRP) remained below 5 mg/L and fecal calprotectin (FCP) below 250 µg/g. The proportion achieving normalization was found to remain stable or increase between weeks 52 and 104.

Endoscopic outcomes at week 104 were most frequently observed with both CRP and FCP normalization at week 64, although rates were similar with FCP normalization alone. The researchers thus noted that biomarker normalization, "especially FCP, may be a reliable predictor of long-term endoscopic response and remission."

Mirikizumab showed sustained efficacy for bowel urgency outcomes, a symptom the researchers described as "under recognized and debilitating," with additional improvements during the second year of treatment.

### Safety

During the second year of treatment, 64.7% of patients experienced treatment-emergent adverse events — most mild or moderate — and 7.7% had serious adverse events.

The most common adverse events were COVID-19 and upper respiratory infections. Adverse events led to treatment discontinuation in 2.6% of patients. One death due to COVID-19 pneumonia occurred in an unvaccinated patient.

### Insights and opportunities

The researchers noted that the study used a treat-through design that did not restrict analyses to induction responders from VIVID-1, aligning with clinical practice and aiming to better understand long-term treatment effects, including among initial nonresponders.

Mirikizumab "showed sustained clinical and endoscopic remission in patients with moderately to severely active Crohn's disease over two years, including among patients who had failed other biologic agents," Dr. Sands said. Patients who had achieved clinical remission at one year "did particularly well," with 92.9% maintaining clinical remission and 87.6% achieving endoscopic response at the end of two years. Mirikizumab also had "an excellent safety profile."

However, the researchers noted several limitations. VIVID-2 is an open-label study without a comparator group, which could influence reporting of outcomes. In addition, most participants were Asian or White, which may limit generalizability to other populations.

Looking ahead, Dr. Sands noted that "as mirikizumab is more widely used, real-world evidence should continue to evaluate the efficacy and safety in broader populations."

*The study was funded by Eli Lilly and Company. Investigators reported multiple industry relationships, including with Eli Lilly.*

# MASLD fibrosis significantly drives HCC risk, study finds

Large patient-level meta-analysis clarifies how fibrosis stage shapes liver cancer risk.

By Doug Brunk

Advanced liver scarring sharply increases the risk of liver cancer in metabolic dysfunction–associated steatotic liver disease (MASLD), new research shows. The finding comes from a large meta-analysis that reconstructed data from nearly 4 million people and provides updated estimates of how risk changes over time.

The study, published in *Clinical Gastroenterology and Hepatology*, pooled data from 26 cohort studies involving 3,995,728 individuals and found that cumulative hepatocellular carcinoma (HCC ) incidence rises steadily over time among patients with MASLD and advanced fibrosis, reaching 8.8% at 10 years in population-based administrative database cohorts and as high as 48.5% in hospital- or clinic-based cohorts.

For the analysis, senior author Daniel Q. Huang, MBBS, MCI, FRCP, of the Division of Gastroenterology and Hepatology in the Department of Medicine at National University Hospital, Singapore, and colleagues conducted a systematic review of Medline and Embase from inception through Nov. 21, 2024, identifying 4,951 articles.

After duplicate removal and screening, 26 studies met eligibility criteria and were included in the quantitative analysis. The researchers reconstructed individual patient time-to-event data from Kaplan–Meier curves reported in each study.

Across database studies, patients with MASLD and advanced fibrosis experienced a cumulative HCC incidence of 0.8% at 1 year, 2.4% at 3 years, 3.9% at 5 years, and 8.8% at 10 years. In contrast, patients without advanced fibrosis had substantially lower cumulative incidence estimates of 0.1%, 0.5%, 0.7%, and 1.3% at the same time points.

Multilevel Cox regression analysis confirmed the strength of this association. The presence of advanced fibrosis was linked to an approximately elevenfold higher risk of developing HCC compared with MASLD without advanced fibrosis in administrative database cohorts.

The pattern was similar but more pronounced in hospital- or clinic-based studies. In these cohorts, cumulative HCC incidence among patients with advanced fibrosis reached 3.9% at 1 year, 11.7% at 3 years, 21% at 5 years, and 48.5% at 10 years. Patients without advanced fibrosis had lower but still notable risks of 1.6%, 4.7%, 8.2%, and 18.3% over the same intervals. Advanced fibrosis in these cohorts was associated with a tenfold increase in HCC risk.

Subgroup analyses also highlighted the influence of cirrhosis. In administrative database studies, cumulative HCC incidence among patients with MASLD and cirrhosis reached 1.4% at 1 year, 4.1% at 3 years, 6.7% at 5 years, and 15.3% at 10 years, compared with 0.1%, 0.3%, 0.4%, and 1.1% among patients without cirrhosis. Cirrhosis increased the risk of HCC more than eightfold in these datasets.

Hospital-based cohorts again showed higher incidence overall. Patients with cirrhosis had cumulative HCC rates of 3.8% at 1 year, 10.3% at 3 years, and 20.5% at 5 years, compared with 0.9%, 2.8%, and 4.6% among those without cirrhosis. Cirrhosis increased the likelihood of HCC development more than twentyfold in these studies.

Researchers analyzed administrative database and hospital-based studies separately because of differences in patient selection and surveillance practices. Patients treated in specialty clinics may have more severe metabolic conditions and may receive cancer screening more often. This could lead to higher reported rates of HCC compared with rates seen in broader population-based datasets.

Sensitivity analyses also examined the effect of MASLD diagnostic methods. Studies that relied on histologic confirmation tended to report higher HCC incidence than those using imaging or administrative coding, which investigators attributed partly to selection bias because patients undergoing biopsy often have more severe disease.

MASLD has become the fastest-growing cause of HCC worldwide, according to the study authors. However, current European Association for the Study of the Liver guidelines say there is not enough evidence to recommend routine HCC screening.

"Further prospective studies will be helpful to discern if HCC surveillance is cost-effective for people with MASLD and advanced fibrosis," the authors concluded.

*Dr. Huang disclosed that he receives funding from the Singapore Ministry of Health's National Medical Research Council and the NUH Clinician Scientist Program.*

*GI & Hepatology News* invited Maya Balakrishnan, MD, MPH, of the Section of Gastroenterology & Hepatology at Baylor College of Medicine, Houston, to weigh in on the study.

### Why is this study important?

**Dr. Balakrishnan:** MASLD is extremely common, and it is one of the fastest-rising causes of HCC. To figure out which patients with MASLD are at most at risk, we need precise, time-based estimates. This study helps address this important public health question. It shows that HCC risk is not uniform across people with MASLD, and that HCC risk in MASLD is concentrated much more heavily in patients with advanced fibrosis and cirrhosis.

### What are the potential clinical implications?

**Dr. Balakrishnan:** The biggest clinical implication is risk stratification. The study supports the idea that fibrosis stage is central when thinking about HCC risk in MASLD. They found that the risk of HCC over 10 years was substantially higher in MASLD with cirrhosis versus without cirrhosis: 8-fold higher in the database studies and 20 times higher in clinic/hospital samples. The analyses also showed that HCC hazard was higher in MASLD with advanced fibrosis versus without.

These findings provide continued evidence that patients with MASLD and cirrhosis need close surveillance. Whether surveillance is needed in people with advanced cirrhosis but without cirrhosis though is still an open question and requires further prospective studies.

### What are the study's key strengths?

**Dr. Balakrishnan:** First, the study includes a very large sample size, incorporating 26 studies and nearly 4 million individuals. Second, the authors used a rigorous analytic approach by reconstructing individual time-to-event data from Kaplan–Meier curves, which allows for a more accurate estimation of cumulative cancer incidence over time. This matters because surveillance decisions depend on how risk accumulates over years, not just whether cancer occurs at any point.

Third, the authors performed a stratified analysis in which administrative database studies were analyzed separately from hospital- or clinic-based cohorts rather than being pooled together. This is important because these populations differ substantially.

### What are the biggest limitations of this research?

**Dr. Balakrishnan:** This study reports pooled incidence drawn from observational cohort studies, not from prospective studies specifically designed to answer a uniform HCC risk question. The findings are therefore informative but cannot by themselves establish surveillance thresholds or prove surveillance benefit.

Other study limitations are standard limitations of most MASLD meta-analyses. For example, heterogeneity in how MASLD and fibrosis were defined across studies —histology, imaging, non-invasive tests, and/or administrative codes. Also, the authors couldn't assess covariates that were not reported in the original studies. Consequently, they could not perform detailed multivariable analyses for additional risk factors that could refine how we think about HCC risk. They also could not conduct competing-risk analyses.

*Dr. Balakrishnan reported having no disclosures.*

Maya Balakrishnan, MD, MPH

# AGA updates MASLD care pathway

Continued From Page 1

Clinicians are advised to screen three main groups: patients with type 2 diabetes; individuals with overweight or obesity plus at least one additional metabolic risk factor; and patients with incidental hepatic steatosis on imaging or elevated aminotransferase levels.

Clinically significant fibrosis occurs in about 14% of overweight or obese individuals and up to 20% of those with MASLD. Among patients with type 2 diabetes and MASLD, roughly 35.5% have advanced fibrosis (F2–F4), according to evidence reviewed by the task force, led by first author Fasiha Kanwal, MD, MSHS, of the Section of Gastroenterology and Hepatology in the Department of Medicine at Baylor College of Medicine, Houston.

Because abdominal ultrasound has limited sensitivity for mild steatosis, the pathway suggests clinicians may proceed directly to fibrosis risk stratification in high-risk populations rather than relying on ultrasound for initial diagnosis.

## Two-step risk stratification

A two-tier strategy is recommended using noninvasive tests to identify patients who require specialty evaluation.

The first step uses the fibrosis-4 (FIB-4) index, calculated from routine laboratory values. A FIB-4 score below 1.3 (or below 2 for patients aged 65 years or older) reliably excludes advanced fibrosis, with negative predictive values of 90% or higher. Patients with low scores can remain in primary care with repeat testing every one to two years. Those with FIB-4 scores at or above these thresholds should undergo second-tier testing.

The second step involves imaging-based liver stiffness measurement, typically vibration-controlled transient elastography. A liver stiffness value below 8 kilopascals indicates low risk for clinically significant fibrosis, whereas values of 8 kPa or higher should prompt referral to hepatology for further evaluation.

When elastography is unavailable, the enhanced liver fibrosis blood test may serve as an alternative, with a cutoff of 9.2 used to detect clinically significant fibrosis.

## Metabolic disease management

Aggressive management of cardiometabolic risk factors for all patients with MASLD, regardless of fibrosis stage, is recommended.

Weight reduction of at least 5% can improve steatosis, while losses of 10% or more are typically required for histologic improvement in liver fibrosis. Pharmacologic therapy is tailored to disease severity and comorbid conditions.

For patients with MASLD at low risk of fibrosis, medications primarily target metabolic disease.

For patients with clinically significant fibrosis, the pathway incorporates newer disease-specific treatments. Resmetirom, a thyroid hormone receptor-β agonist approved for MASH with F2–F3 fibrosis, improved both resolution and fibrosis in the phase 3 MAESTRO-NASH trial, with resolution rates of about 26%–30% compared with 9.7% in the placebo group.

Semaglutide has also demonstrated benefits in the phase 3 ESSENCE trial, achieving MASH resolution without worsening fibrosis in 63% of treated patients versus 34% of those receiving placebo.

## Implementation challenges

Despite growing evidence and new therapies, real-world adoption of MASLD care pathways remains inconsistent. Barriers they cited include limited awareness among primary care clinicians, competing clinical priorities, and variability in access to noninvasive testing.

To address these challenges, the updated pathway includes a pragmatic implementation framework designed to help health systems integrate screening and management algorithms into routine workflows.

## Clinical implications

The key takeaway is the importance of systematic screening and staged evaluation using widely available noninvasive tests. Early identification of fibrosis allows clinicians to initiate targeted therapy and surveillance before complications such as cirrhosis or hepatocellular carcinoma develop.

With MASLD prevalence rising and new treatments entering clinical practice, the pathway aims to standardize care across specialties and improve outcomes for a growing population of patients with metabolic liver disease, noted the authors.

*Dr. Kanwal is an investigator at the Institute for Clinical and Translational Research and the Veterans Administration Center for Innovations in Quality, Effectiveness, and Safety at the Michael E. DeBakey VA Medical Center, Houston. She is supported in part by the National Cancer Institute and the Cancer Prevention & Research Institute of Texas. Disclosures for the other study authors are available in the published study.*

*GI & Hepatology News* invited invited Brian DeBosch MD, PhD, AGAF, Professor and Co-Division Chief of Gastroenterology, Hepatology & Nutrition at Indiana University School of Medicine, to weigh in on the care pathway.

**In your opinion, what are the top clinical takeaways from this clinical care pathway?**

**Dr. DeBosch:** Important changes in whom to screen, how to screen, and how to treat are included in this new pathway. The overall goal is to clarify which patients warrant screening, condense screening steps where it makes sense, and incorporate new, field-changing RCT data and FDA-approved therapies in the care pathway. This is a more complete and data-driven pathway than its first iteration.

The new pathway indicates that patients with overweight or obesity should be screened with at least one cardiometabolic risk factor. However, patients with isolated overweight or obesity should not be routinely assessed based on recently published data.

The new pathway streamlined how to screen. For example, the simplified screening cutoffs using the Fibrosis-4 (FIB-4) score is simplified to 1.3 for patients under 65, whereas patients who previously would have been labeled with an "indeterminant" FIB-4 value (1.3-2.67) range can now be functionally considered to have a positive screen. Similarly, new data confirm the value under 8.0 kPa as an appropriately sensitive cutoff to demarcate low- and high-risk fibrosis in patients. Finally, the option is afforded to skip two-tiered screening in some high-risk (e.g. T2DM or patients evaluated in a referral center) in favor of single-step FibroScan screening and diagnosis.

Perhaps the most notable addition is the incorporation of new, gold-standard RCT data for novel FDA-approved MASH therapy that were reported in the interval since the original pathway. Prior therapies were limited by a paucity of evidence for efficacy, lack of significant weight-directed control. Now, resmetirom and semaglutide demonstrate efficacy in reversing hepatic fibrosis and inflammation, whereas semaglutide and tirzepatide demonstrate robust weight loss and insulin sensitization.

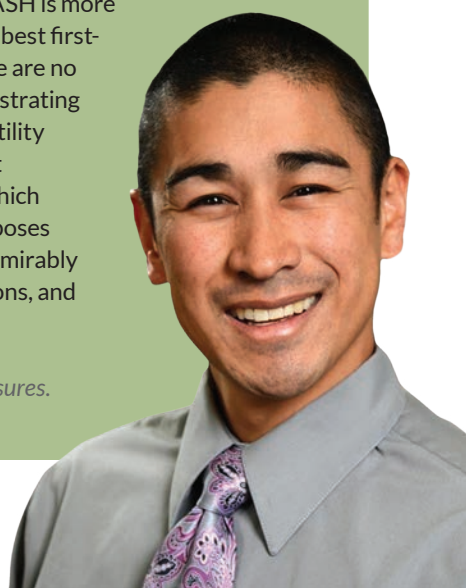
**How might this care pathway affect patient care?**

**Dr. DeBosch:** The new pathway streamlines and simplifies screening pathways and are quite directive in treatment recommendations. This makes diagnosing and treating MASH in the primary care setting more accessible, which might expand the overall population accessing care for this common and morbid disease.

**What knowledge gaps remain, and what research should be done next?**

**Dr. DeBosch:** There are at least three important gaps, ideally in the next pathway. First, how should we treat so-called "lean" MASH? Current agents are aimed at reducing intrahepatic fat and/or peripheral adiposity. However, it is possible that lean MASH is more immunologically driven, making the choice of best first-line agent less straight-forward. Second, there are no agents with published, large RCT data demonstrating reversal of F4 compensated cirrhosis. Thus, utility of deploying currently available agents in that population is not clear. Third, the degree to which the pathway applies equally to all settings exposes the larger issue. The authors rightfully and admirably acknowledge disparities in Hispanic populations, and worsened outcomes in Black patients.

*Dr. DeBosch reported having no relevant disclosures.*



Brian DeBosch MD, PhD, AGAF


# FDA approves linerixibat for cholestatic pruritus in PBC

Linerixibat "is an added therapy that's mechanistically different from what we have, and therefore I think that it's going to be used."

By Doug Brunk

The FDA has approved linerixibat (Lynavoy), the first therapy in the US specifically indicated for cholestatic pruritus in adults with primary biliary cholangitis (PBC), addressing a long-standing gap in symptom management.

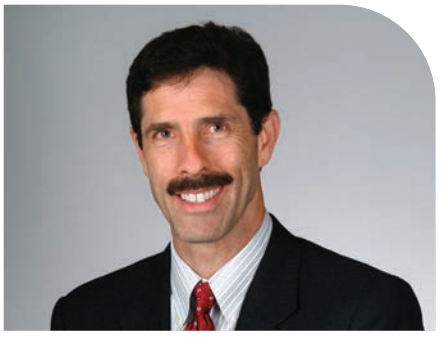
Cholestatic pruritus affects up to 89% of patients with PBC and can be severe and persistent. It frequently disrupts sleep, exacerbates fatigue, and significantly impairs quality of life. In some cases, patients pursue liver transplantation primarily due to intractable itching rather than liver failure.

Approval was based on results from the phase III GLISTEN trial, a randomized, placebo-controlled study demonstrating statistically significant improvements in itch severity and itch-related sleep interference. Reductions in worst itch scores were observed as early as 2 weeks and were sustained through 24 weeks. The findings suggest the treatment works quickly.

Although absolute reductions in itch scores were modest on a numerical rating scale, they were associated with clinically meaningful patient-reported improvements, including better sleep. For hepatologists and gastroenterologists, these quality-of-life gains are particularly relevant given the substantial burden of pruritus.

The most common adverse events in GLISTEN were gastrointestinal, including diarrhea (61%) and abdominal pain (18%), typically mild to moderate. Approximately 4% of patients discontinued treatment because of diarrhea. According to a GSK media release, patient counseling regarding tolerability will be important.

Linerixibat's mechanism also highlights the broader role of bile acid signaling in symptom generation and raises the possibility of similar approaches in other cholestatic conditions. Regulatory reviews are ongoing in multiple regions, suggesting potential expansion into global practice.



Don C. Rockey, MD

In an interview with *GI & Hepatology News*, Don C. Rockey, MD, who chairs the Department of Medicine at the Medical University of South Carolina (MUSC), Charleston, characterized the approval of linerixibat as "a significant advance."

"Right now, we throw sort of the kitchen sink at these patients," said Dr. Rockey, who is also Vice Chair of AGA Institute Council Liver & Bilary Section. "They might get Benadryl or an SSRI. Sometimes that works and sometimes it doesn't. So, I think this is going to be targeted to patients with moderate-to-severe, and especially, I think, severe pruritus."

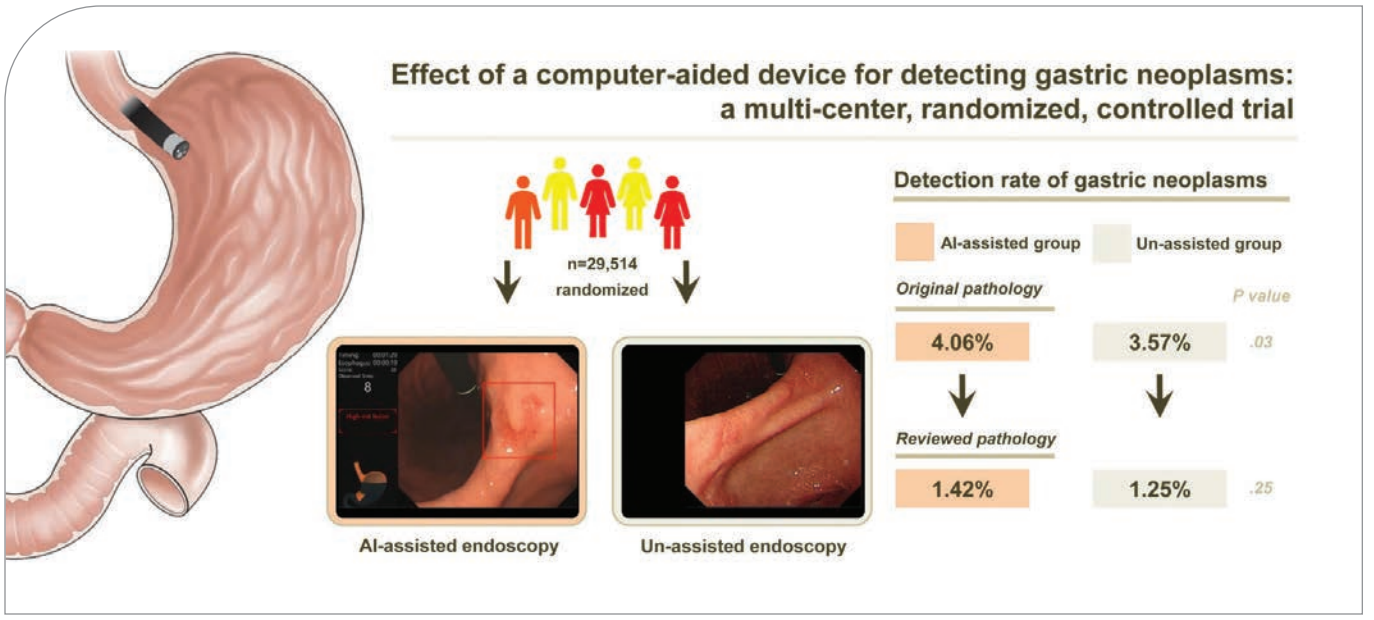
Linerixibat "is an added therapy that's mechanistically different from what we have, and therefore I think that it's going to be used," he noted.

*Dr. Rockey disclosed that he has conducted clinical trials on behalf of the MUSC for pharmaceutical companies, including GSK.*

# AI system offers no benefit in upper endoscopy, study finds

"Our study is the first to underscore the critical role of rigorous pathologic review in evaluating AI systems."

By Amy Pfeiffer




Artificial intelligence (AI) assistance during upper endoscopy did not significantly improve the detection of gastric neoplasms after centralized pathology review in a large multi-center randomized controlled trial, although the system reduced blind spots and increased inspection time.

"Our study is the first to underscore the critical role of rigorous pathologic review in evaluating AI systems," noted Zehua Dong, PhD, of the Department of Gastroenterology at Renmin Hospital of Wuhan University in China, and colleagues.

The study, published in *Gastroenterology*, enrolled 29,514 patients undergoing esophagogastroduodenoscopy (EGD) at 24 hospitals across 12 provinces in China between December 2021 and November 2023. Patients were randomized to AI-assisted EGD using the ENDOANGEL-GN system or standard EGD without AI assistance. The primary endpoint was the detection rate of gastric neoplasms after centralized endoscopic and pathologic review.

In the intention-to-treat cohort, gastric neoplasms were detected in 1.42% of patients in the AI-assisted group compared with 1.25% in the control group, indicating no statistically significant difference.

When outcomes were assessed using the original pathology reports from participating centers, the AI-assisted group showed a higher detection rate (4.06% vs 3.57%). This difference was not significant after centralized pathology review. However, "subgroup analysis suggested potential benefit among less experienced endoscopists and during fatigue periods," wrote Dr. Dong and colleagues.

The trial also found substantial reclassification of dysplasia diagnoses during centralized pathology review. After expert review, 83.58% of lesions initially diagnosed as low-grade intraepithelial neoplasia and 14% of those diagnosed as high-grade intraepithelial neoplasia were reclassified as benign. In contrast, only 0.72% of lesions initially considered non-neoplastic were later reclassified as neoplasms.

Secondary outcomes showed no significant differences between groups in early gastric cancer detection or in detection of intestinal metaplasia and/or gastric atrophy in the intention-to-treat analysis after pathology review.

The AI-assisted system significantly reduced the number of blind spots during endoscopy, with an average of 1.07 blind spots in the AI group compared with 2.52 in the control group. Procedure time and inspection time were longer in the AI-assisted group (7.69 vs 7.33 minutes, respectively).

In exploratory subgroup analyses, AI assistance was associated with a higher detection rate of gastric neoplasms among endoscopists with less than three years of experience (1.44% vs 0.78%).

The investigators also evaluated the diagnostic performance of the AI system in lesion recognition. In the experimental group, ENDOANGEL-GN identified 100% of pathologically confirmed gastric adenocarcinoma, 91.9% of high-grade intraepithelial neoplasia, and 57.1% of low-grade intraepithelial neoplasia. False-positive alerts were most commonly associated with chronic inflammation, intestinal metaplasia, gastric atrophy, and other benign mucosal findings.

The authors noted that the study population included a high proportion of tertiary hospitals and experienced endoscopists, which may have influenced the results.

"The findings highlight the critical impact of centralized pathologic review on the evaluation of AI performance. Subgroup analyses suggest that AI may provide advantages in specific clinical scenarios, underscoring the importance of optimizing AI applications in targeted clinical settings," concluded investigators.

*They disclosed having no conflicts of interest.*

*GI & Hepatology News* invited Mimi Tan, MD, MPH, an assistant professor in the Section or Gastroenterology at Baylor College of Medicine, Houston, Texas, to comment on the study.

**This randomized trial found that AI assistance during upper endoscopy did not significantly improve gastric neoplasm detection after centralized pathology review. How should clinicians interpret these findings?**

**Dr. Tan:** This clinical trial is important for gastroenterologists to consider as we evaluate computer-assisted detection (CADe) models for indications beyond colon polyp detection. However, the findings must be interpreted in the context of several key limitations.

Several CADe systems for gastric cancer and precancer detection have been developed in Asia, and ENDOANGEL is among the most extensively published. Despite the impressive scale of this trial, the primary outcomes deserve scrutiny. Like many other CADe systems, ENGOANGEL was trained on retrospectively collected image and video datasets, often without complete ground-truth histopathology for all patients and was optimized using expert endoscopist image interpretation as the reference standard. Thus, when AI models are applied to scenarios where the true endpoint requires histopathology (e.g., early gastric cancer or dysplasia), there is inherent mismatch between what the system was trained to recognize (visual pattern) and the trial outcome (tissue diagnosis).

With that being said, I am still optimistic that there is a role for CADe models in upper GI indications. Unlike our Asian counterparts, we, as US endoscopists, have far less clinical exposure to early gastric cancer, dysplasia, and intestinal metaplasia detection in routine practice. Thus, the potential for improvement in endoscopic detection with AI assistance could be higher in our setting. Even if a CADe system fails to move the needle in a high-volume Chinese screening center staffed by expert endoscopists, it may offer meaningful gains in a US practice where recognizing subtle early gastric lesions is not a routine competency.

**The study also showed substantial reclassification of dysplasia diagnoses after expert pathology review. What does this reveal about the challenges of evaluating AI systems for cancer detection?**

**Dr. Tan:** The study demonstrated a significant reclassification of dysplasia diagnoses following expert pathology review, which exposes a critical challenge in evaluating AI systems: the reliability of the "ground truth." Similarly, there was a dramatic drop in gastric neoplasia diagnosis rates from 3.57% tp 4.06% by local pathologists to 1.25% to 1.42% when the same slides were interpreted by the central study pathologists. This exposes a foundational vulnerability in the entire CADe development pipeline. If the histopathology labels used as the ground truth have questionable accuracy, the CADe models trained on them will be equally unreliable. Therefore, establishing standardized, centralized expert pathology review is essential for both training and evaluating AI model performance in clinical settings.

**Although detection rates were similar, AI assistance reduced blind spots and increased inspection time. Do you view these changes as meaningful improvements in endoscopy quality?**

**Dr. Tan:** The secondary outcomes showing reduction in blind spots and longer inspection times are meaningful improvements. These improvements in quality metrics may provide specific advantages in certain scenarios. The CADe model may help bridge the experience gap (gastric neoplasm detection among endoscopists with less than three years' experience) or mitigating human error during times of fatigue. Subgroup analyses suggested AI may benefit less experienced endoscopists.

*"If we want models to accurately detect histopathology-based diseases, the training dataset of images and videos must be paired with undisputed ground truth histopathology."*

**Do you see a potential role for AI as a training or decision-support tool in endoscopy?**

**Dr. Tan:** An important conclusion from this trial is the benefit of AI assistance for less experienced endoscopists. CADe for gastric cancer detection has been shown to have comparable performance to expert endoscopists and may even surpass less experienced endoscopists; CADe models could help equalize performance across different skill levels.

Conversely, there are growing concerns about "de-skilling" (clinicians losing diagnostic competencies due to over-reliance on AI) or "never skilling" (never developing diagnostic competencies due to exposure to AI early on in training). While AI models can serve as a valuable training or decision-support tool, endoscopists must be careful not to become too overly dependent on the technology. It is essential to maintain personal diagnostic proficiency even while utilizing AI to improve detection.


**Based on these results, what additional evidence or improvements would be needed before AI-assisted systems could be widely adopted for gastric cancer detection?**

**Dr. Tan:** There is a clear role for CADe models to assist with detection of gastric cancers and precancers in US practice settings where these conditions are not routinely encountered by the gastroenterologist. But the trustworthiness of these CADe models is only as good as their training data. If we want models to accurately detect histopathology-based diseases, the training dataset of images and videos must be paired with undisputed ground truth histopathology. We saw in this trial that a massive discrepancy in ground truth histopathology (original vs revised histopathology) determined whether the primary outcome was positive or negative. Moving forward, we must ensure CADe model training pipelines incorporate rigorous, centralized pathologic review to establish a truly reliable gold standard.

# Esophageal care, reexamined: Dilation, dysmotility, and diagnostic debates

***Dear colleagues,***

Much of our clinical practice focuses on the diagnosis and management of upper gastrointestinal disorders, ranging from dysphagia due to mechanical obstruction to dyspepsia and abdominal pain related to dysmotility disorders. While presentations vary, patients consistently seek both an accurate diagnosis and durable relief.

In this issue, Dr. William Ravich shares practical insights on performing successful esophageal dilation of benign stenoses, addressing controversial topics such as the role of the barium esophagram — is it obsolete? — and the often quoted "rule of threes."

Drs. Aylin Tansel and Yamini Natarajan examine upper GI dysmotility, reviewing the spectrum of medical therapies and outlining their approach to the nuanced care these patients require. We hope these contributions address common concerns and enhance your clinical practice in treating these disorders.

*Gyanprakash A. Ketwaroo, MD, MSc, is associate professor of medicine, Yale University, New Haven, and chief of endoscopy at West Haven VA Medical Center, both in Connecticut. He is an associate editor for GI & Hepatology News.*

## Management of esophageal dysmotility: A pragmatic, phenotype-based approach

By Aylin Tansel, MD, and Yamini Natarajan, MD

### Introduction

Esophageal dysmotility can be a challenging disorder to manage. Despite advances in esophageal testing to categorize esophageal motility disorders, therapeutic management remains notably limited for esophageal disorders outside of achalasia. We have found the best approach is to evaluate the presence of five domains: hypomotility, hypercontractility or spasticity, hypersensitivity, reflux, and finally, other factors (such as medications, structural issues, dysmotility). By focusing on the processes of influencing dysmotility, care becomes more intentional and impactful.

### Hypomotility

Disorders of weak motility, including ineffective esophageal motility and absent peristalsis, are commonly encountered in patients with chronic reflux or connective tissue disorders. Because of the decreased contractility, bolus transit relies heavily on esophageal diameter and gravity. Pharmacologic options are limited and off label, but can be effective for some patients, ideally before meals for optimal effect. Prokinetic agents include bethanechol, pyridostigmine, and buspirone. In addition to pharmacologic therapy, lifestyle modifications such as smaller bites, staying upright, and walking after meals can provide substantial benefits. Empiric esophageal dilation should be considered in patients with predominantly solid food dysphagia because of the reliance on gravity to aid in food bolus clearance. These patients are at risk for significant reflux-particularly supine reflux; antireflux teaching is essential.

### Hypercontractility and spasm

For the management of hypercontractile and spastic disorders (jackhammer esophagus or distal esophageal spasm), the goal is to promote smooth muscle relaxation and thereby relieve symptoms of dysphagia and/or chest pain. Eating habits should be assessed, with emphasis on slow, thorough chewing, as rapid eating can exacerbate hypercontractility and spasticity. For acute relief of chest pain and/or dysphagia, sublingual formulations are preferred. Peppermint oil can be a safe initial trial. For most with dysphagia/pain, consider prescribing an antispasmodic (hyoscyamine). Severe spasms may require escalation to nitrates, such as nitroglycerin. For patients with frequent symptoms (with most meals), calcium channel blockers (diltiazem, nifedipine) can be taken prior to meals to reduce contraction amplitudes and thereby improve symptoms. For patients nonresponsive to medical management, consider esophageal Botox and possible dilation. Some patients may benefit from specialized tailored therapy (such as POEM, Heller myotomy, etc). A low threshold to refer to tertiary centers is recommended.

### Hypersensitivity

Symptoms of chest pain or discomfort can be particularly vexing for both provider and patient. If symptoms occur while eating, a hypercontractile or spastic esophagus may be the culprit, and management as outlined above can be considered. If worse after meals, suspect reflux. If constant and refractory to above, then the treatment can become more complicated involving the gut-brain axis. Short acting agents such as sucralfate or antacid-lidocaine mixtures can be used on demand for immediate symptom control but have limited long-term utility. For patients with predominant symptoms of chest pain, neuromodulators can be an effective tool. Tricyclic antidepressants have the best evidence for functional esophageal disorders. Other options include SSRIs, SNRIs, gabapentinoids, or trazodone. For isolated globus symptoms, consider a one-time gentle proximal esophageal dilation to see if this improves symptoms, and if fails, then consider trial with a gabapentinoid. Collaboration with a therapist and psychiatrist with expertise in functional gastrointestinal disorders can also be beneficial.

### Reflux

Reflux can be both a cause and consequence of esophageal dysmotility. When reflux symptoms are present, they should be categorized by severity, frequency, and timing — whether postprandial, supine, or both. For postprandial symptoms, diaphragmatic breathing after meals and during acute episodes can be emphasized. For supine symptoms, left-sided or upright sleeping positions and avoidance of late meals are recommended.

The type of symptoms reported is also important. Regurgitation typically does not improve with acid suppression, whereas chest pain or burning may respond. If chest pain or burning persist despite optimized acid suppression, consideration can be given to possible bile reflux. For atypical symptoms such as cough or voice hoarseness, efforts should focus on reducing nighttime reflux, including elevating the head of the bed and considering a short trial of twice-daily PPI therapy. These patients may benefit from a multidisciplinary approach involving ENT and pulmonary specialists.

### External and Systemic Influences

Finally, it is always important to step back and evaluate if any other factors could be further contributing to esophageal dysmotility. For instance, carefully review medications that can affect esophageal motility, such as opioids. If patients are on opioids, coniser peripherally acting mu-opioid receptor antagonists to help decrease the impact of opioids on esophageal dysmotility. The size and structure of pills are also important to consider. Large tablets can trigger symptoms, become impacted, and result in pill esophagitis.

Consider alternate formulations such as liquids, crushed tablets, or open capsules whenever feasible. Consideration should be given to structural issues of the esophagus (e.g., epiphrenic diverticulum, peptic stricture, Schatzki ring), surrounding structures (such as a large left atrium or cervical hardware), and additional anatomical factors that may influence reflux or impair emptying (including hiatal hernia or prior surgeries). Treatment of these structural factors can often yield significant symptom improvement. Finally, evaluation of additional dysmotility issues, such as gastroparesis or constipation, can yield an additional target to optimize symptoms, particularly for patients with significant reflux.

## Conclusion

Ultimately, the management of esophageal dysmotility is far more effective when we stop treating it as a single diagnosis and instead approach it as a set of underlying physiologic problems. It is helpful to focus on the processes influencing dysmotility — hypomotility, hypercontractility or spasticity, sensitivity, reflux, and other external or systemic factors. The goal is to improve how patients eat, feel, and function. This framework simplifies decision-making and helps align treatment more closely with patient symptoms.

*Dr. Tansel practices at the University of Pittsburgh, Department of Medicine, Division of Gastroenterology.*

*Dr. Natarajan practices at the Kelsey-Seybold Clinic in Houston, TX.*

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# Is the esophagram obsolete?

By William J. Ravich, MD

A few years ago, I was asked to speak on the topic "Is the esophagram obsolete." The answer, to paraphrase Mark Twain, is that the report of the esophagram's demise is grossly exaggerated.

In my experience, the most frequent reason for the misdiagnosis or missed diagnosis in patients with dysphagia is the failure to perform a high-quality barium esophagram. Guidelines that reduce the esophagram to either secondary, or even optional, status are misguided. Endoscopy as the initial study is most appropriate for patients who have solid food dysphagia localized to the chest. These are patients with a high probability of a stricture beyond the cervical esophagus. Even in this situation, I have one proviso for skipping an esophagram; if no stenotic lesion is found on visual exam, the endoscopist must go ahead and dilate on an empiric basis. For most other dysphagia patients, a barium esophagram is a better choice for the initial evaluation. The esophagram should be tailored to the clinical question posed by the patient's clinical presentation.

Pharyngeal dysphagia should include a dynamic (video) evaluation of the pharynx in addition to the traditional esophagram. The gastroenterologist should make it a habit of reviewing the images with a focus on missed findings (it happens more than I would like to admit) and deficiencies in the examination (areas of inadequate distension in which a stenotic lesion might be hiding).

## The "Rule of Three"

The "Rule of Three" states that you should "only dilate by three increments" (in dilator size) at a single session. Often attributed to H. Worth Boyce, MD, a legendary esophagologist, Boyce denied originating the rule, and believed he received the concept from his own mentor Eddy David Palmer, MD. Although superficially straight-forward, it contains a number of ambiguities.

**What diameter dilator should you start with?** I once had the opportunity of sharing my concerns about the rule with Dr. Boyce over lunch. He indicated that in practice he starts counting increments at the size at which he first appreciates "moderate resistance" — a rather subjective criterion.

**What increments does the rule refer to?** Depending on the manufacturer and type of dilator, dilators are sold in increments that vary from 2, 3, or 4 French units (1 French unit is equivalent to 1/3 mm in diameter). At the Johns Hopkins Hospital, where I cut my teeth as an endoscopist, non-guided serial dilators were available in 4 French increments. I only discovered later that they were available in 2 French increments. The brand of guidewire-directed dilators was sold in 3 French increments. So did the "Rule of Three" require limiting dilation to 2, 3, or 4 mm at a single session?

**And how does the rule apply to balloon dilators?** The reality is: it doesn't! During the same discussion, Worth agreed that the rule couldn't be applied to balloon dilators where the dilators don't provide the type of tactile sense of resistance upon which the rule depends.

**Does the "Rule of Three" matter?** A retrospective study found that the risk of perforation does not appear to increase when the rule is not followed, so there appears to be at least some leeway in applying the rule in endoscopic practice. My approach is that as long as I sense no more than mild to moderate resistance, I will continue to dilate up to my ultimate goal for dilation. On the other hand, if I detect a significant jump in resistance at any point, and if I have already achieved a 4 mm dilation, I complete the passage of the dilator in my hand and then stop. When in doubt, I stop!

## Schatzki's Rule

Richard Schatzki, in his seminal work on the distal esophageal ring that bears his name, reported that rings that were 12 mm or less in diameter (as measured on an esophagram) always caused dysphagia, whereas those that were greater than 20 mm, rarely (he didn't actually say never) cause dysphagia. Extrapolating this to strictures in general, the goal of dilation is to either resolve symptoms or to achieve a luminal diameter of 20 mm. In practice, a target of 18 mm with further dilation at a separate session up to 20 mm if symptoms persist, seems reasonable and consistent with Schatzki's findings.

## Solid food dysphagia

A common wisdom in gastroenterology is that solid food dysphagia is "a stricture until proven otherwise." The problem is: what is required to prove otherwise? An esophagram can miss a stenotic lesion and passage of a barium tablet (typically only 13 mm in diameter), does not exclude the presence of a significant stenosis (see the discussion of Schatzki's Rule, above). Similarly, a clinically significant stenosis can be missed at endoscopy, especially when it occurs in the area of the PE segment or EG junction, regions where non-distensibility may be unappreciated or accepted as reflecting sphincter function. Another common wisdom — that "if the scope passes through there is not a significant stenosis," — is clearly incorrect, as the standard endoscopy is only 9-10 mm in diameter. Empiric dilation of the EG junction for symptoms that are clearly esophageal in nature, and of both the EG junction and PE segment when a cricopharyngeal dysfunction is also a possibility, represents the definitive proof that a stricture is — or is not— present. One advantage of a balloon dilator is that withdrawal of a fully inflated 20 mm balloon from the stomach to, or when symptoms warrant, through the PE segment, may unmasked a stenosis segment or resistant PE segment that was not appreciated during visual examination. If no resistance is encountered, a clinically significant esophageal stricture has effectively been excluded.

*Dr. Ravich is a professor of medicine in the Department of Internal Medicine/Section of Digestive Diseases at Yale School of Medicine, New Haven, CT.*

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# Feeding the gut: How Nancee Jaffe is advancing nutrition in gastroenterology

**GI dietitians help patients reclaim food as nourishment and enjoyment, not something to fear.**

For many patients with digestive disorders, food can feel like both the problem and the solution. Few clinicians understand that balance better than Nancee Jaffe, MS, RDN, CSDH, founding registered dietitian for the UCLA Vatche and Tamar Manoukian Division of Digestive Diseases. Since joining UCLA in 2012, Jaffe has helped build a comprehensive GI Nutrition Program that supports patients with complex digestive conditions while educating fellows, gastroenterologists, and other health care professionals about the evolving role of nutrition in gastrointestinal care.

Beyond UCLA, Jaffe leads a growing private practice, Nancee Jaffe & Associates Nutrition Services, where she and her team counsel patients with conditions including celiac disease, inflammatory bowel diseases, disorders of gut–brain interaction, and gastrointestinal manifestations of long COVID and dysautonomia. A national speaker and leader in the field, she also helped formalize DIGID (Dietitians in Gluten and Gastrointestinal Disorders), a GI-focused dietitian group jointly housed within AGA and the Academy of Nutrition and Dietetics in 2020, and she serves as a committee lead for the Rome Foundation Diet and Nutrition Section.

In this spotlight, Jaffe reflects on her unexpected path into gastrointestinal nutrition, the growing role of dietitians on the GI care team, and why helping patients rebuild a healthy relationship with food can be just as important as managing symptoms.

**What first drew you to the field of gastrointestinal nutrition, and how did that path lead you to UCLA?**

**Dr. Jaffe:** My deep interest in the digestive tract began in 2002 after I contracted a parasite during a study abroad program in Ecuador. The parasite remained in my body for about a year and a half and grew to roughly 1.5 feet long. After it passed, I began experiencing a range of unexpected and disruptive symptoms, including dizziness, fainting spells, extreme hunger, depression, bloating, weight loss, indigestion, and diarrhea.

After seeing seven doctors and spending six years searching for answers, I was finally diagnosed with celiac disease. Within two weeks of starting a strict gluten-free diet, all my symptoms disappeared.

Feeling so dramatically better — and remembering how long and difficult my diagnostic journey had been — motivated me to become a health care professional who could help others with gastrointestinal disorders. During graduate school, I completed one of my dietetic internships with the UCLA Division of Digestive Diseases, and I was fortunate that they later invited me to stay on as their first GI-specialized dietitian.

**For gastroenterologists who may not work closely with dietitians, what does a GI-specialized dietitian bring to the care team that differs from general nutrition counseling?**

**Dr. Jaffe:** Expert GI dietitians play many roles on the care team. In many ways, we act as detectives — listening closely to patients' symptoms, reviewing their diet and eating patterns, and identifying potential food triggers without unnecessarily over-restricting their diets.

We also bring evidence-based knowledge that helps cut through the overwhelming amount of nutrition information available today. Both patients and providers are often exposed to conflicting advice, and GI dietitians help translate current research into practical strategies.

Another important role is serving as a bridge between medical recommendations and everyday life. We help translate clinical guidance into realistic and sustainable dietary approaches.

For many patients, food becomes something they fear. They worry that every bite may trigger pain, bloating, or an urgent trip to the bathroom. That fear can spiral into restrictive eating patterns or even disordered eating. A GI-specialized dietitian helps patients reclaim food as nourishment and enjoyment — not something to fear — while still managing digestive symptoms.

**Nutrition is often one of the first things patients ask about when they receive a GI diagnosis. How do you help patients navigate the overwhelming amount of diet advice available online?**

**Dr. Jaffe:** Much of my work involves helping patients filter through the noise. There is an enormous amount of diet advice online, and much of it is contradictory or unsupported by evidence.

*"When patients understand how to use nutrition without fear, they don't just feel better — they feel empowered."*

Top Right: Jaffe reviewing clinical notes with a colleague.
Bottom Right: Jaffe and colleagues after a symposium session at DDW.
Bottom Left: Jaffe unwinding with colleagues at a DDW event in Chicago.

I help patients understand what science shows, what might apply to their specific condition, and what is likely unnecessary or overly restrictive. My goal is to help patients build a balanced, sustainable approach to eating that improves symptoms without creating unnecessary fear around food.

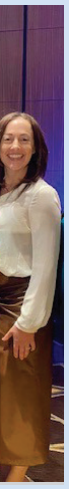
**What are some of the most common misconceptions about diet and digestive health?**

**Dr. Jaffe:** One of the most common misconceptions is that food causes IBS, or that there is a "perfect" diet that can cure it. Patients often say, "If I avoid gluten, dairy, or fiber — or eat more fiber — maybe my IBS will go away."

The truth is that food does not cause IBS, and there is not a single cure-all diet. However, nutrition can play an important role in managing symptoms and improving quality of life.

Many patients also believe they need allergy testing, food sensitivity panels, or extreme elimination diets to control symptoms. Digestive issues are complex. Food can certainly act as a trigger, but symptoms often arise from a gut that is already hypersensitive.

This means the same food may feel fine one day and trigger another. Helping patients understand this variability can take pressure off their food choices and allow for a more balanced, flexible approach to diet.



**Where do you see nutrition therapy having the greatest impact on patient outcomes or quality of life?**

**Dr. Jaffe:** Patients often want diet to play a role in managing their disease because it is something they feel they can control. Helping patients find the right balance between dietary changes and acceptance of the role diet plays in their condition can be incredibly powerful.

When patients understand the evidence and learn how to use nutrition to improve their quality of life, they feel empowered. At the same time, recognizing that diet is rarely a cure-all can relieve pressure and reduce unnecessary food restrictions.

Instead of labeling foods as "good" or "bad," we can help patients think about foods as everyday choices, special-occasion foods, or foods that may be better tolerated in smaller portions or with evidence-based tools like digestive enzymes.

**The role of GI-focused dietitians has grown significantly in recent years. What factors do you think are driving that shift?**

**Dr. Jaffe:** As more research emerges demonstrating the impact of diet on digestive symptoms and quality of life, interest in nutrition as a component of treatment has grown.

At the same time, patients have always wanted guidance on diet. We all eat every day, and our relationship with food plays a significant role in our health and well-being. Creating a diet that is balanced, adequate, enjoyable, and supportive of healing can make a meaningful difference for many GI patients.

In addition, increased attention to the gut microbiome and the role of prebiotics and probiotics has brought even more focus to the relationship between food, gut health, and overall wellness.

**What barriers still exist to integrating GI dietitians into clinical practice, and what changes would help make this type of care more widely available?**

**Dr. Jaffe:** One major challenge is the limited number of dietitians with specialized expertise in GI disorders, which restricts access for patients who could benefit from targeted nutrition therapy. Misconceptions about insurance coverage also play a role; many patients and providers assume that nutrition services are not covered.

At the same time, certain insurers — including Medicare — do not reimburse medical nutrition therapy for many GI conditions. Additionally, misinformation from social media influencers and other media sources can undermine evidence-based dietary guidance and create confusion for patients.

Finally, some health care providers still underestimate the value of including a dietitian as part of the multidisciplinary GI care team. Expanding specialized training opportunities, improving insurance coverage and reimbursement, addressing misinformation, and increasing provider awareness could all help make GI dietitian services more widely accessible.

**When should a gastroenterologist consider referring a patient to a GI-specific dietitian?**

**Dr. Jaffe:** The short answer is almost anytime diet comes up in a clinical visit.

Whenever dietary concerns are discussed, a referral to a GI-specialized dietitian can be valuable. A brief conversation or a one-page handout is rarely enough to address patients' diet-related questions.

There's a reason dietitians often spend 60–90 minutes during an initial consultation. Diet is complex, personal, and emotionally significant. Patients benefit from a thorough, individualized discussion rather than quick recommendations delivered during a busy clinic visit.

## Lightning round

**What are you excited about working on right now?**

Building my private practice with two expert dietitian associates and serving as a board member on the UCLA Integrative Digestive Health Program Education Committee.

**Favorite quote or words to live by?**

The Voltaire quote: "Perfect is the enemy of good."

**Biggest misconception about your career?**

That dietitians just tell patients to eat more vegetables — or that discussing diet is easy. We act as detectives, understand pathophysiology, and provide evidence-based, yet practical, guidance.

**Best way to unwind after work?**

Exercise. I love to dance and take long walks.

**Favorite AGA memory?**

Helping build the alliance between AGA and the Academy of Nutrition and Dietetics in 2020.

**Describe your dream retirement.**

Living in a small forest town with lots of rain and plenty of time for reading and making art.

**Favorite hobby?**

Bookbinding. I apprentice once a month with a master bookbinder in Hollywood, CA.

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