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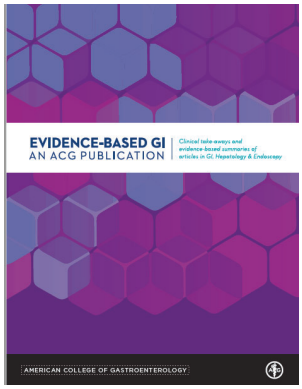

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INDICATION

IBSRELA (tenapanor) is indicated for the treatment of Irritable Bowel Syndrome with Constipation (IBS-C) in adults.

IMPORTANT SAFETY INFORMATION

WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS

IBSRELA is contraindicated in patients less than 6 years of age; in nonclinical studies in young juvenile rats administration of tenapanor caused deaths presumed to be due to dehydration. Avoid use of IBSRELA in patients 6 years to less than 12 years of age. The safety and effectiveness of IBSRELA have not been established in patients less than 18 years of age.

CONTRAINDICATIONS

- IBSRELA is contraindicated in patients less than 6 years of age due to the risk of serious dehydration.
- IBSRELA is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction.

WARNINGS AND PRECAUTIONS

Risk of Serious Dehydration in Pediatric Patients

- IBSRELA is contraindicated in patients below 6 years of age. The safety and effectiveness of IBSRELA in patients less than 18 years of age have not been established. In young juvenile rats (less than 1 week old; approximate human age equivalent of less than 2 years of age), decreased body weight and deaths occurred, presumed to be due to dehydration, following oral administration of tenapanor. There are no data available in older juvenile rats (human age equivalent 2 years to less than 12 years).
- Avoid the use of IBSRELA in patients 6 years to less than 12 years of age. Although there are no data in older juvenile rats, given the deaths in younger rats and the lack of clinical safety and efficacy data in pediatric patients, avoid the use of IBSRELA in patients 6 years to less than 12 years of age.

Diarrhea

Diarrhea was the most common adverse reaction in two randomized, double-blind, placebo-controlled trials of IBS-C. Severe diarrhea was reported in 2.5% of IBSRELA-treated patients. If severe diarrhea occurs, suspend dosing and rehydrate patient.

MOST COMMON ADVERSE REACTIONS

The most common adverse reactions in IBSRELA-treated patients (incidence ≥2% and greater than placebo) were: diarrhea (16% vs 4% placebo), abdominal distension (3% vs <1%), flatulence (3% vs 1%) and dizziness (2% vs <1%).

Reference: IBSRELA [prescribing information]. Waltham, MA: Ardelyx, Inc.; 2022.

Please see Brief Summary of full Prescribing Information on the following page.

ardelyx

IBSRELA (tenapanor) tablets, for oral use

Brief Summary of Full Prescribing Information

WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS

- **IBSRELA is contraindicated in patients less than 6 years of age; in nonclinical studies in young juvenile rats administration of tenapanor caused deaths presumed to be due to dehydration [*see Contraindications (4), Use in Specific Populations (8.4)*].**
- **Avoid use of IBSRELA in patients 6 years to less than 12 years of age [*see Warnings and Precautions (5.1), Use in Specific Populations (8.4)*].**
- **The safety and effectiveness of IBSRELA have not been established in patients less than 18 years of age [*see Use in Specific Populations (8.4)*].**

1 INDICATIONS AND USAGE

IBSRELA is indicated for treatment of irritable bowel syndrome with constipation (IBS-C) in adults.

4 CONTRAINDICATIONS

IBSRELA is contraindicated in:

- Patients less than 6 years of age due to the risk of serious dehydration [*see Warnings and Precautions (5.1), Use in Specific Populations (8.4)*].
- Patients with known or suspected mechanical gastrointestinal obstruction.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Serious Dehydration in Pediatric Patients

IBSRELA is contraindicated in patients below 6 years of age. The safety and effectiveness of IBSRELA in patients less than 18 years of age have not been established. In young juvenile rats (less than 1 week old; approximate human age equivalent of less than 2 years of age), decreased body weight and deaths occurred, presumed to be due to dehydration, following oral administration of tenapanor. There are no data available in older juvenile rats (human age equivalent 2 years to less than 12 years).

Avoid the use of IBSRELA in patients 6 years to less than 12 years of age. Although there are no data in older juvenile rats, given the deaths in younger rats and the lack of clinical safety and efficacy data in pediatric patients, avoid the use of IBSRELA in patients 6 years to less than 12 years of age [*see Contraindications (4), Warnings and Precautions (5.2), Use in Specific Populations (8.4)*].

5.2 Diarrhea

Diarrhea was the most common adverse reaction in two randomized, double-blind, placebo-controlled trials of IBS-C. Severe diarrhea was reported in 2.5% of IBSRELA-treated patients [*see Adverse Reactions (6.1)*]. If severe diarrhea occurs, suspend dosing and rehydrate patient.

6 ADVERSE REACTIONS

6.1 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 with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described below reflect data from 1203 adult patients with IBS-C in two randomized, double-blind, placebo-controlled clinical trials (Trial 1 and Trial 2). Patients were randomized to receive placebo or IBSRELA 50 mg twice daily for up to 52 weeks. Demographic characteristics were comparable between treatment groups in the two trials [*see Clinical Studies (14)*].

Most Common Adverse Reactions

The most common adverse reactions reported in at least 2% of patients in IBSRELA-treated patients and at an incidence greater than placebo during the 26-week double-blind placebo-controlled treatment period of Trial 1 are shown in Table 1.

Table 1: Most Common Adverse Reactions* in Patients With IBS-C in Trial 1 (26 Weeks)

Adverse Reactions	IBSRELA N=293 %	Placebo N=300 %
Diarrhea	16	4
Abdominal Distension	3	<1
Flatulence	3	1
Dizziness	2	<1

*Reported in at least 2% of patients in IBSRELA-treated patients and at an incidence greater than placebo.

The adverse reaction profile was similar during the 12-week double-blind placebo-controlled treatment period of Trial 2 (610 patients: 309 IBSRELA-treated and 301 placebo-treated) with diarrhea (15% with IBSRELA vs 2% with placebo) and abdominal distension (2% with IBSRELA vs 0% with placebo) as the most common adverse reactions.

Adverse Reaction of Special Interest – Severe Diarrhea

Severe diarrhea was reported in 2.5% of IBSRELA-treated patients compared to 0.2% of placebo-treated patients during the 26 weeks of Trial 1 and the 12 weeks of Trial 2 [*see Warnings and Precautions (5.2)*].

Patients with Renal Impairment

In Trials 1 and 2, there were 368 patients (31%) with baseline renal impairment (defined as eGFR less than 90 mL/min/1.73m^2). In patients with renal impairment, diarrhea, including severe diarrhea, was reported in 20% (39/194) of IBSRELA-treated patients and 0.6% (1/174) of placebo-treated patients. In patients with normal renal function at baseline, diarrhea, including severe diarrhea, was reported in 13% (53/407) of IBSRELA-treated patients and 3.5% (15/426) of placebo-treated patients. No other differences in the safety profile were reported in the renally impaired subgroup.

The incidence of diarrhea and severe diarrhea in IBSRELA-treated patients did not correspond to the severity of renal impairment.

Adverse Reactions Leading to Discontinuation

Discontinuations due to adverse reactions occurred in 7.6% of IBSRELA-treated patients and 0.8% of placebo-treated patients during the 26 weeks of Trial 1 and the 12 weeks of Trial 2. The most common adverse reaction leading to discontinuation was diarrhea: 6.5% of IBSRELA-treated patients compared to 0.7% of placebo-treated patients.

Less Common Adverse Reactions

Adverse reactions reported in less than 2% of IBSRELA-treated patients and at an incidence greater than placebo during the 26 weeks of Trial 1 and the 12 weeks of Trial 2 were: rectal bleeding and abnormal gastrointestinal sounds.

Hyperkalemia

In a trial of another patient population with chronic kidney disease (defined by eGFR from 25 to 70 mL/min/1.73m^2) and Type 2 diabetes mellitus, three serious adverse reactions of hyperkalemia resulting in hospitalization were reported in 3 patients (2 IBSRELA-treated patients and 1 placebo-treated patient).

7 DRUG INTERACTIONS

7.1 OATP2B1 Substrates

Tenapanor is an inhibitor of intestinal uptake transporter, OATP2B1 [*see Clinical Pharmacology (12.3)*]. Drugs which are substrates of OATP2B1 may have reduced exposures when concomitantly taken with IBSRELA. Monitor for signs related to loss of efficacy and adjust the dosage of concomitantly administered drug as needed.

Enalapril is a substrate of OATP2B1. When enalapril was coadministered with tenapanor (30 mg twice daily for five days, a dosage 0.6 times the recommended dosage), the peak exposure (C_{max}) of enalapril and its active metabolite, enalaprilat, decreased by approximately 70% and total systemic exposures (AUC) decreased by approximately 50% to 65% compared to when enalapril was administered alone [*see Clinical Pharmacology (12.3)*].

Monitor blood pressure and increase the dosage of enalapril, if needed, when IBSRELA is coadministered with enalapril.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Tenapanor is minimally absorbed systemically, with plasma concentrations below the limit of quantification (less than 0.5 ng/mL) following oral administration [*see Clinical Pharmacology (12.3)*]. Therefore, maternal use is not expected to result in fetal exposure to the drug. The available data on IBSRELA exposure from a small number of pregnant women have not identified any drug associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes. In reproduction studies with tenapanor in pregnant rats and rabbits, no adverse fetal effects were observed in rats at 0.1 times the maximum recommended human dose and in rabbits at doses up to 8.8 times the maximum recommended human dose (based on body surface area).

Data

Animal Data

In an embryofetal development study in rats, tenapanor was administered orally to pregnant rats during the period of organogenesis at dose levels of 1, 10 and 30 mg/kg/day. Tenapanor doses of 10 and 30 mg/kg/day were not tolerated by the pregnant rats and was associated with mortality and moribundity with body weight loss. The 10 and 30 mg/kg dose group animals were sacrificed early, and the fetuses were not examined for intrauterine parameters and fetal morphology. No adverse fetal effects were observed in rats at 1 mg/kg/day (approximately 0.1 times the maximum recommended human dose) and in rabbits at doses up to 45 mg/kg/day (approximately 8.8 times the maximum recommended human dose, based on body surface area).

In a pre- and post-natal developmental study in mice, tenapanor at doses up to 200 mg/kg/day (approximately 9.7 times the maximum recommended human dose, based on body surface area) had no effect on pre- and post-natal development.

8.2 Lactation

Risk Summary

There are no data available on the presence of tenapanor in either human or animal milk, its effects on milk production or its effects on the breastfed infant. Tenapanor is minimally absorbed systemically, with plasma concentrations below the limit of quantification (less than 0.5 ng/mL) following oral administration [*see Clinical Pharmacology (12.3)*]. The minimal systemic absorption of tenapanor will not result in a clinically relevant exposure to breastfed infants. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for IBSRELA and any potential adverse effects on the breastfed infant from IBSRELA or from the underlying maternal condition.

8.4 Pediatric Use

IBSRELA is contraindicated in patients less than 6 years of age. Avoid IBSRELA in patients 6 years to less than 12 years of age [*see Contraindications (4), Warnings and Precautions (5.1)*].

The safety and effectiveness of IBSRELA in patients less than 18 years of age have not been established.

In nonclinical studies, deaths occurred in young juvenile rats (less than 1-week-old rats approximate human age equivalent of less than 2 years of age) following oral administration of tenapanor, as described below in Juvenile Animal Toxicity Data.

Juvenile Animal Toxicity Data

In a 21-day oral dose range finding toxicity study in juvenile rats, tenapanor was administered to neonatal rats [post-natal day (PND) 5] at doses of 5 and 10 mg/kg/day. Tenapanor was not tolerated in male and female pups and the study was terminated on PND 16 due to mortalities and decreased body weight (24% to 29% reduction in females at the respective dose groups and 33% reduction in males in the 10 mg/kg/day group, compared to control).

In a second dose range finding study, tenapanor doses of 0.1, 0.5, 2.5, or 5 mg/kg/day were administered to neonatal rats from PND 5 through PND 24. Treatment-related mortalities were observed at 0.5, 2.5, and 5 mg/kg/day doses. These premature deaths were observed as early as PND 8, with majority of deaths occurring between PND 15 and 25. In the 5 mg/kg/day group, mean body weights were 47% lower for males on PND 23 and 35% lower for females on PND 22 when compared to the controls. Slightly lower mean tibial lengths (5% to 11%) were noted in males and females in the 0.5, 2.5, and 5 mg/kg/day dose groups on PND 25 and correlated with the decrements in body weight noted in these groups. Lower spleen, thymus, and/or ovarian weights were noted at the 0.5, 2.5, and 5 mg/kg/day doses. Tenapanor-related gastrointestinal distension and microscopic bone findings of increased osteoclasts, eroded bone, and/or decreased bone in sternum and/or femorotibial joint were noted in males and females in the 0.5, 2.5, and 5 mg/kg/day dose groups [*see Contraindications (4), Warnings and Precautions (5.1)*].

8.5 Geriatric Use

Of the 1203 patients in placebo-controlled clinical trials of IBSRELA, 100 (8%) were 65 years of age and older. No overall differences in safety or effectiveness were observed between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

10 OVERDOSAGE

Based on nonclinical data, overdose of IBSRELA may result in gastrointestinal adverse effects such as diarrhea as a result of exaggerated pharmacology with a risk for dehydration if diarrhea is severe or prolonged [*see Warnings and Precautions (5.1)*].

17 PATIENT COUNSELING INFORMATION

Advise the patients to read the FDA-approved patient labeling (Medication Guide).

Diarrhea

Instruct patients to stop IBSRELA and contact their healthcare provider if they experience severe diarrhea [*see Warnings and Precautions (5.2)*].

Accidental Ingestion

Accidental ingestion of IBSRELA in children, especially children less than 6 years of age, may result in severe diarrhea and dehydration. Instruct patients to store IBSRELA securely and out of reach of children [*see Contraindications (4), Warnings and Precautions (5.1)*].

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EVIDENCE-BASED GI
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Stemming the Tide: Is Long-Acting Octreotide Injection Better Than Standard of Care for Angiodysplasia-Related GI Bleeding?

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Associate Editor

This summary reviews reviews Goltstein L, Grooteman KV, Bernts LH et al. Standard of care versus octreotide in angiodysplasia-related bleeding: a multicenter randomized control trial. Gastroenterology 2024;155: 690-703.

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Keywords: GI hemmorrhage, small bowel bleeding, angiectasia

STRUCTURED ABSTRACT

Question: Does 40 mg octreotide long-acting release injected intramuscularly every 28 days reduce transfusion requirements compared to standard of care in patients with recurrent bleeding from gastrointestinal (GI) angiodysplasia?

Design: Randomized, open-label, multicenter, parallel-group, superiority study conducted between September 2015 and April 2021.

Setting: Seventeen hospitals (15 peripheral and 2 academic medical centers) in the Netherlands.

Patients: Adults with transfusion-dependent anemia due to endoscopically

confirmed angiodysplasias who had received at least 1 endoscopic treatment and at least 4 transfusion units (parenteral iron or red blood cell transfusions) in the preceding year.

Intervention: Participants received 2 intramuscular long-acting octreotide intramuscular [IM] injections of 20 mg (40 mg in total) every 28 days for 52 weeks versus standard of care, which was defined as oral iron supplementation.

Patients in both groups could receive endoscopic therapy with argon-plasma coagulation (APC) of angiodysplasias, discontinuation of antithrombotics, and tranexamic acid. If standard of care was deemed inadequate in this open-label study, then patients could be switched to octreotide, but this was considered a protocol violation.

Red blood cell (RBC) transfusion was performed per the following thresholds: individuals with severe co-morbidities and hemoglobin (hgb) <9.5g/dl; individuals with symptomatic anemia and fewer co-morbidities and hgb <8 g/dl; and healthy individuals with asymptomatic anemia with hgb <6.5g/dl.

Outcomes: The primary outcome was the mean difference in blood and parenteral iron requirements (units) between the intervention and standard-of-care group. Blood requirement was defined as red blood cell transfusions per 500 cc or packed cells, while iron requirements were defined as intravenous iron infusions per 500 mg. Secondary outcomes included the proportion of participants in both groups that experienced ≥ 50% (good response) and 100% (full response) reduction in the number of transfusion units received during the study year compared to the baseline. Other secondary outcomes included serum hemoglobin and ferritin levels.

Data Analysis: Analyses were performed based on both intention-to-treat and per-protocol. Analyses of covariance were used to compare the number of transfusion units, endoscopy procedures, bleeding episodes, healthcare utilization, fatigue levels, and quality of life.

Funding: The trial was funded by Novartis between 2015 and 2019, and then by the Netherlands Organization for Health Research and Development between 2019 and 2022.

Results: Sixty-two patients were randomized: 52% male; mean age-72 years old; location of angiodysplasia-small intestine (87%), colon (48%), stomach (27%);

and concurrent antiplatelet or anticoagulant use was approximately 80% in both groups. No patients withdrew from the study but 7 died before study completion.

During the 52-week treatment period, octreotide-treated patients received a mean adjusted number of transfusion requirements of 11 vs 21.2 in the standard of care group (difference of 10.2, 95% 2.4-18.1, *P*=0.01) (Table 1). A good treatment response, defined as ≥50% reduction in transfusion requirements, was observed in 61% of patients in the octreotide group vs 19% of patients in the standard of care group. A full response, defined as 100% reduction in transfusion requirements, was observed in 19% of the octreotide group vs 3% in the standard-of-care group. Mean endoscopy utilization was also lower in the octreotide group (0.3 vs 1.2, adjusted difference of 0.9; 95% confidence interval [CI] 0.3-1.5), as were the number of bleeding episodes (adjusted difference 3.2; 95% CI, -0.2 to 6.6). Octreotide-related adverse events (AEs) included pain at the site of administration, diarrhea, abdominal pain, and glucose intolerance. Serious AEs were reported in 2 patients on octreotide including acute cholangitis and symptomatic hypoglycemia.

	Octreotide (n=31)	Standard of Care (n=31)	Difference
Transfusion units	11.0 (5.5–16.5)	21.2 (15.7–26.7)	10.2 (2.4–18.1) *P=0.12
RBC transfusion	8.2 (3.2–13.2)	16.8 (11.8–21.8)	8.6 (1.4–15.7)
IV iron transfusions	2.8 (1.3–4.3)	4.6 (3.1–6.0)	1.8 (0.3–3.9)
Transfusion decrease ≥50%	19/31 (61)	6/31 (19)	13/31 (42)
Transfusion decrease 100%	5/19 (26)	1/6 (17)	
Bleeding episodes	5.3 (2.9–7.6)	8.5 (6.1–10.8)	3.2 (0.2 to 6.6)
Hospital admissions	0.5 (0.2 to 1.1)	1.8 (1.2–2.5)	1.3 (0.4–2.3)

Table 1: Octreotide vs standard of care (outcomes of intention-to-treat analysis).

IV, intravenous; RBC, red blood cells.

COMMENTARY

Why Is This Important?

In the last year, the therapeutic landscape for angiodysplasia-related GI bleeding has been met with new level 1 evidence from international randomized trials that medical therapies including thalidomide.[1,2] and octreotide improve outcomes. In this multicenter trial from the Netherlands Goltstein et al, provide the best evidence so far that the somatostatin analog, octreotide, at a dose of 40 mg administered every 28 days reduces transfusion requirements compared to the standard of care.

Somatostatin analogs are believed to reduce angiodysplasia-related GI bleeding by decreasing blood flow to the splanchnic vasculature in the GI tract. Prior studies on somatostatin analogs have mostly been small and observational in design.[3] Endoscopic therapies, hitherto regarded as the mainstay of treatment, are associated with high rebleeding rates. Chen et al, in a recent study, showed that thalidomide reduced the risk of recurrent bleeding at doses of 50 mg and 100 mg after treatment for 4 months, compared with placebo.[2] While the anti-angiogenic effects of thalidomide led to a reduction in rebleeding risk, they also reported side effects such as constipation, limb numbness, and dizziness in 71% of patients which could potentially impact its use in the real world.[2] Concerns about axonal neuropathy with long-term thalidomide use also exist.[4] Importantly, in the United States, thalidomide may not be as widely available for prescription. Due to its widespread use, octreotide may be easier to obtain and its availability in long-acting depot formulation may increase patient compliance. Importantly, in this study, patients on antithrombotic therapy, including antiplatelets and anticoagulation monotherapy, were included.

Key Study Findings

Octreotide treatment was associated with a significant reduction in the number of transfusion requirements by 10.2 (95% CI: 2.4-18.1, P=0.01) among patients with angiodysplasia-related GI bleeding. This benefit was obvious as early as the first month of treatment and persisted for the duration of the study.

In addition, patients in the octreotide group were more likely to achieve a full treatment response with complete resolution of need for transfusion. Severe adverse events were seen in 2 patients receiving octreotide, and the study drug was discontinued in 1 of these patients.

Caution

From a study design perspective, one limitation of the trial was the lack of blinding. As such, the investigators and patients were aware of the treatment. In addition, the study used a relatively high dose of octreotide of 40mg IM, which the investigators allude could explain higher dose-related AEs compared to

prior studies. High-dose continuous octreotide infusion has also been associated with cardiac arrhythmia, but this has not been reported among patients with intermittent dosing which was used in this study. Race and ethnicity data were also not reported which may limit secondary generalizability.

My Practice

In my clinical practice, we offer deep enteroscopy to patients with angiodysplasia-related GI bleeding. Despite the availability of this endoscopic resource, we still see a significant number of readmissions especially among the subgroup of patients on anticoagulation and/or antiplatelet therapy. The study by Golstein et al offers promise that these patients have lower transfusion requirements with octreotide use which is practice changing. Octreotide offers an option that can be easily prescribed using a monthly depot formulation with side effects that are mostly self-limiting, which increases medication adherence and compliance. Based on the recommendations of the investigators, I will probably use octreotide IM at the higher dose for recurrent bleeding after argon plasma coagulation, or when endoscopy is contraindicated. For practitioners that don't have access to double-balloon enteroscopy, they may consider this first-line therapy after confirming small intestinal arteriovenous malformations by capsule endoscopy if patients require recurrent RBC transfusions, especially if the patient is using antithrombotic agents that can't be discontinued. I'd reserve thalidomide for patients who fail octreotide therapy since it's harder to access and is associated with more adverse events.

For Future Research

We now have 2 adequately powered clinical trials supporting the benefits of thalidomide and octreotide for angiodysplasia-related GI bleeding.[1,2] Future studies could consider head-to-head comparisons of thalidomide and octreotide, including efficacy in reducing angiodysplasia-related GI bleeding and side effect profiles. More research is needed on the efficacy of lower octreotide doses and the feasibility of combination with thalidomide.

Conflict of Interest

Dr. Okafor reports no conflicts of interest.

Note: One of the authors of the published article are active on social media. Tag them to discuss their work and this EBGI summary.

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Joost PH Drenth

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Multi-Target Stool RNA Test for CRC Screening: When Should You Use It?

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Editor-in-Chief

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This summary reviews Barnell EK, Wurtzler EM, La Rocca J, et al. Multitarget stool RNA for colorectal cancer screening. JAMA 2023;330:1760-68 .

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Keywords: colorectal cancer screening, stool test, fecal immunochemical test

STRUCTURED ABSTRACT

Question: What is the sensitivity and specificity of a multi-target stool RNA test (ColoSense; Geneoscopy, St. Louis, MO) for colorectal cancer (CRC) screening for detection of stage I, II, and III CRC and advanced adenomas in average-risk individuals aged 45 years and older?

Design: Prospective, blinded, cross-sectional observational diagnostic test study using colonoscopy as the gold standard for detection of CRC and precancerous lesions: CRC-PREVENT study.

Setting: The United States.

Patients: Asymptomatic individuals ≥ 45 years old were first recruited using social media and completed a survey to ensure eligibility for CRC screening. Key exclusion criteria included: (a) history of inflammatory bowel disease (IBD); (b) prior history of adenomas or gastrointestinal (GI) cancers; (c) medical or family history of inherited polyposis syndromes; and, (d) currently up-to-date with CRC screening (e.g., had a normal screening colonoscopy ≤9 years or negative fecal immunochemical test [FIT] within previous year). Individuals with family history of CRC in a first-degree relative were also included.

Interventions/Exposure: Stool specimens for next-generation multi-target stool RNA test were obtained prior to colonoscopy bowel preparation and mailed for processing. The multi-target stool RNA test consists of FIT and concentration of 8 RNA transcripts in stool plus self-reported smoking history (never vs prior or current use of tobacco products). A software program generated the multi-target stool RNA binary result (positive or negative) based on a predetermined threshold value.

After providing the stool specimen, patients were "navigated" using a decentralized nursing call center to have screening colonoscopy prescribed by their health care provider and performed by a local endoscopist.

Outcomes: Primary outcome was sensitivity for CRC and advanced adenomas, defined as adenomas $\geq$ 10 mm, adenoma with villous histology or high-grade dysplasia, and specificity for all other findings. Secondary outcome was sensitivity for advanced adenomas and comparison of FIT and multi-target stool RNA test for CRC and advanced precancerous lesions.

Data Analysis: Sensitivity (percentage of individuals with the disease who have a positive test) and specificity (percentage of individuals without the disease who have a negative test) with corresponding 95% confidence intervals (CIs) were calculated with standard formulas.*

Funding: Geneoscopy, manufacturer of multi-target stool RNA test, ColoSense.

Results: Between June 2021 and June 2022, 11,034 patients provided an adequate stool sample and met enrollment criteria with 85% completing an adequate colonoscopy. Among these individuals, approximately 514 were withdrawn due to inadequate records or being found to meet exclusion criteria, leaving 8,920 patients for evaluation. Demographic data for these patients included: mean age 55 years old, 59% female, 83.5% White, 6.5 % had family history of CRC in first-degree relative, and prior/current user of tobacco products was 34%. In this group, 0.4% (36 out of 8,920) had CRC stage I-III and 6.8% (606 out of 8,920) had advanced adenomas. Overall, adenoma detection rate was 40.1%.

For CRC Stage I-III, 94.4% (34 out of 36) had a positive multi-target stool RNA test. Per the study, sensitivity did not vary substantially based on disease stage or location in the colon. For advanced adenomas, 45.9% (278 out of 606) had a positive multi-target stool RNA test (**Table 1**). FIT had 77.8% sensitivity for Stage I-III CRC and 28.9% sensitivity for advanced adenomas (**Table 1**). The multi-target stool RNA test was significantly better than FIT for both comparisons by McNemar's test. Among 5,345 patients with no adenomas on colonoscopy, specificity of multi-target stool RNA test was 86.9%; 95% CI: 86%-88% (4,647 out of 5,345 had negative test) and specificity for FIT was 95.4%; 95% CI: 95%-96% (5,100 out of 5,345 had negative test).

*Note: Based on US Food and Drug Administration (FDA) guidance provided to study investigators, a test was considered acceptable if sensitivity for CRC was 90% with the lower boundary of the 95% CI for CRC sensitivity was ≥80% and if sensitivity for advanced adenomas was at least 45% with the lower boundary of the 95% CI for advanced adenoma sensitivity was ≥40%, and if specificity for all other findings was ≥80%.

Disease	Sensitivity of Stool DNA	Sensitivity of FIT
Stage I-III CRC	94.4% (95% CI: 81-99)	77.8% (95% CI: 61-90)
Advanced adenomas	45.9% (95% CI 42-50)	28.9% (95% CI: 25-33)

Table 1. Sensitivity of next generation multi-target stool RNA test and FIT.

Abbreviations: CI, confidence interval; CRC, colorectal cancer; FIT, fecal immunochemical test

COMMENTARY

Why Is This Important?

As discussed in prior commentaries,[1-2] about 60% of the eligible US population are up-to-date with CRC screening. This equates to more than 40 million individuals who are not up-to-date with this preventable cancer.[3] Given the desire of some patients to avoid colonoscopy with the associated bowel preparation, sedation, and time missed from work, stool-based tests for CRC screening are a viable option. Although annual FIT is inexpensive for healthcare systems, the sensitivity for stage I-III CRC is 65%-75% (i.e., approximately 25%-35% of individuals with stage I-III CRC will have a negative test). The limited sensitivity of FIT could be overcome by performing it annually, but multiple studies demonstrate that adherence to annual FIT is at best 75% and then decreases to approximately 30%-35% in subsequent years.[3-4] Therefore, stool-based tools with improved sensitivity and higher adherence would be beneficial, and multi-target stool DNA tests fit this need. Although they are more expensive than FIT, the out-of-pocket cost to eligible patients with Medicare, Medicaid, or most commercial insurers is zero since multi-target stool DNA tests are endorsed by the US Preventive Services Task Force and covered as an approved cancer screening test under the Affordable Care Act.

In the study by Barnell et al, new technology examining concentrations of 8 RNA transcriptions in stool are combined with FIT and smoking history to produce a positive or negative test.

These investigators[5] have proposed that eukaryotic RNA derived from stool may be an ideal biomarker to detect CRC and adenomas because it provides an assessment of cellular activity. This is a timely topic since the FDA approved the multitarget stool RNA test in May 2024. However, out-of-pocket cost to patients will probably be substantial unless the US Preventive Services Task Force endorses this test for CRC screening, leading to it being covered as an approved cancer screening test under the Affordable Care Act. Stay tuned.

Key Study Findings

For CRC stage I-III, 94.4% (34 out of 36) had a positive multi-target stool RNA test. Per the study, sensitivity did not vary substantially based on disease stage or location in the colon. For advanced adenomas, 45.9% (278 out of 606) had a positive multi-target stool RNA test (**Table 1**). FIT had 77.8% sensitivity for stage I-III CRC and 28.9% sensitivity for advanced adenomas.

Caution

A substantial proportion of patients completed the stool collection but didn't complete colonoscopy during the study, which creates some uncertainty. The study results are similar to results achieved with multi-target stool DNA, but these tests were not studied head-to-head. Appropriate intervals between multi-target stool RNA tests will need to be better defined by longitudinal data.

My Practice

Again, per prior commentaries,[1-2] colonoscopy is my primary tool for CRC screening since it's also a CRC prevention tool. Nevertheless, some average-risk individuals are fearful of colonoscopy, sedation, or simply doing the bowel preparation and want a non-invasive alternative. What's the best option for these individuals? Again, the best option is the one that the patient actually completes! At my Veteran's Affairs institution, I'm limited to offering annual FITs as a stool-based screening test. Multi-target stool DNA tests clearly produce higher sensitivity than FIT for stage I-III CRC and advanced precancerous lesions,[2] are essentially free to most patients, and only have to be completed once every 3 years. Until multi-target stool RNA tests are covered by insurance, I'd stick with FIT or multi-target stool DNA tests if your patient is hesitant to get colonoscopy.

For Future Research

Innovations in RNA technology to improve specificity (i.e., minimizing frequency of false positive tests, which drives use of colonoscopy) while preserving high sensitivity for CRC and advanced adenomas will be beneficial. A comparative trial with multi-target stool DNA tests would define if one test is more accurate than the other. Until then, defer to stool-based tests that are covered with no out-of-pocket costs to the patient.

Conflicts of Interest

Dr. Schoenfeld previously served as a speaker for Exact Sciences and has discontinued that relationship.

Note: The authors of this study are active on social media. Tag them to discuss their work and this EBGI summary.

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EVIDENCE-BASED GI
AN ACG PUBLICATION

ENDOSCOPY

Can IV Metoclopramide Improve Endoscopic Visualization for Patients with Active Upper Gastrointestinal Bleeding?

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This summary reviews Vimonsuntirungsri T, Thungsuk R, Nopjaroonsri P, et al. The efficacy of metoclopramide for gastric visualization by endoscopy in patients with active upper gastrointestinal bleeding: double-blind randomized controlled trial. Am J Gastroenterol 2024;119(5):846-855.

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Keywords: metoclopramide, upper GI bleed, RCT, endoscopy

STRUCTURED ABSTRACT

Question: What is the efficacy of metoclopramide compared to placebo for gastric visualization in patients with active upper gastrointestinal bleeding (UGIB)?

Design: Double-blind, placebo-controlled randomized controlled trial (RCT).

Setting: Two medical centers in Thailand: the King Chulalongkorn Memorial Hospital, Sawanpracharak Hospital.

Patients: Adults ≥ 18 years with active UGIB (defined as having fresh or bright red blood within 24 hours or fresh blood during gastric lavage) who arrived in the emergency department and had an upper endoscopy within 12 hours after arrival. Adults were excluded if they had known prior gastric or duodenal surgery; known esophageal, gastric, or duodenal cancer; advanced HIV; and pregnant.

Interventions: Metoclopramide 10 mg administered intravenously between 30 to 120 minutes before the upper endoscopy. The comparison group was normal saline.

Outcomes: The primary outcome was the percentage of patients with adequate visualization in the metoclopramide group compared with the placebo group as determined by the Frossard scoring method. Secondary outcomes were the mean difference in endoscopic visualized gastroduodenal scores (EVS), duration of esophagogastroduodenoscopy (EGD), immediate hemostasis, the need for a second look EGD within 72 hours after initial endoscopy, unit of blood transfusion, length of hospital stay, and 30-day rebleeding rate.

Data Analysis: Intention-to-treat analysis. In addition, logistic regression was used to estimate the impact of treatment on adequate visualization.

Funding: The Gastroenterological Association of Thailand (GAT).

Results: Sixty-two patients (31 metoclopramide and 31 placebo) were enrolled and analyzed (**Figure 1**). The percentage of patients with adequate visualization was higher in the metoclopramide group versus in the placebo group (77.4% vs 61.6%, respectively; odds ratio [OR] 2.16 [0.71-6.58], *P*=0.16) but was not statistically significant. However, in gastric lesion subgroup analysis, metoclopramide improved the adequate visualization rate compared to placebo (92.9% vs 50%; OR 13.0 [1.32-128.10], *P*=0.03) and improved endoscopic visualization at the fundus. Lastly, metoclopramide reduced the need for second look EGD within 72 hours compared to placebo (3.2% vs 22.6%; OR -0.11 [0.01-0.99], *P*=0.02).

COMMENTARY

Why Is This Important?

Acute upper gastrointestinal bleed (UGIB) is a common problem worldwide and is associated with significant morbidity and mortality.[1] Endoscopy and its therapeutic interventions have been shown to reduce both rebleeding rates and mortality rates associated with acute UGIB.[2] However, the effectiveness of endoscopic interventions for an UGIB is dependent on the quality of endoscopic visualization, which can be hampered by the presence of blood, clots, or other residues in the stomach and duodenum. Although current guidelines, including those pubished by the American College of Gastroenterology and European Society of Gastrointestinal Endoscopy,[2,3] suggest the use of intravenous (IV) erythromcyin before

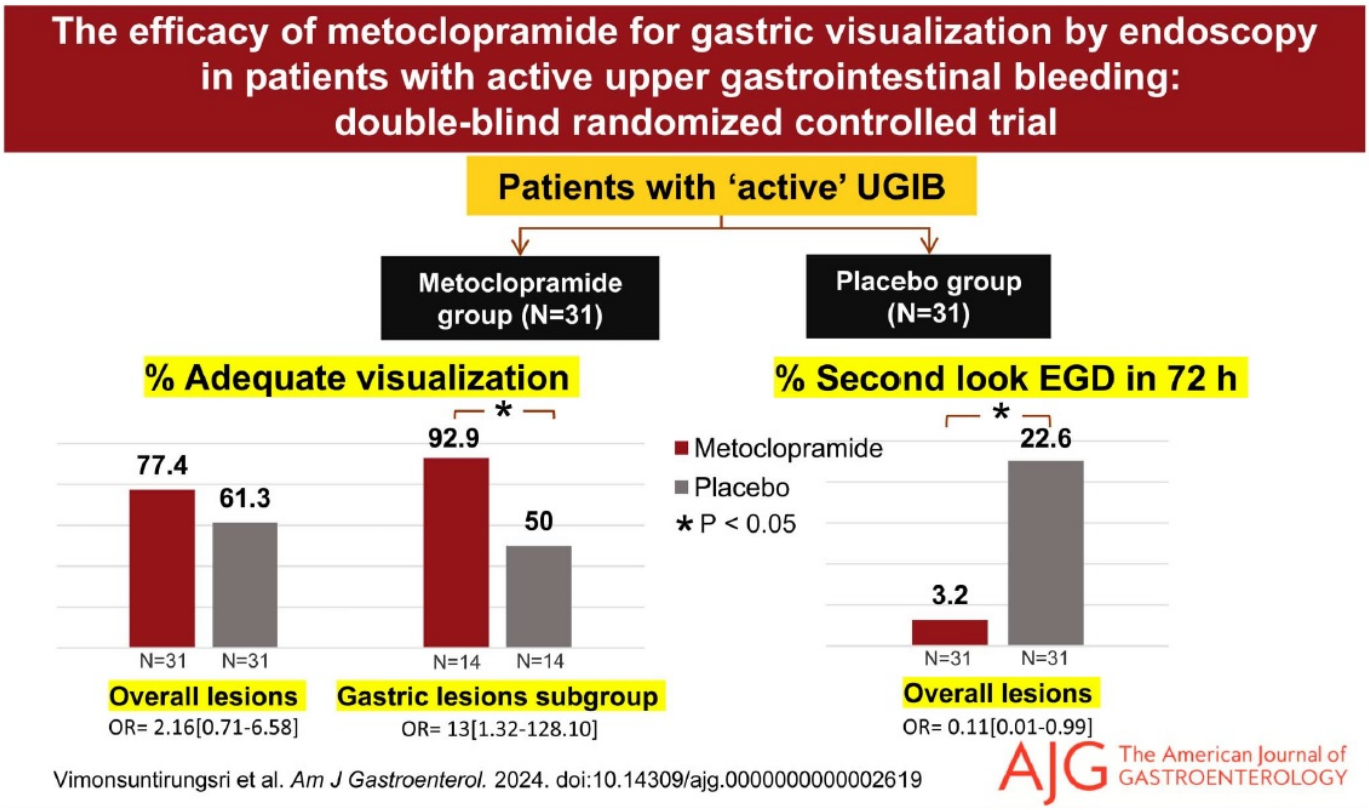

Figure 1. Visual abstract showing results.

endoscopy for an acute UGIB, it can prolong the QT interval, which can be associated with ventricular tachyarrhythmias and Torsade de Points. Thus, identifying a prokinetic agent that has rapid onset, easily accessible, and is safe and effective is urgently needed for the management of acute UGIBs. Therefore, this RCT from Vimonsuntirungsri and colleagues addresses this gap by evaluating the use of metoclopramide for gastric visualization during endoscopy in patients with acute UGIB.[4]

Key Study Findings

Overall, metoclopramide did not significantly improve endoscopic visualization among patients with acute UGIB. However, in subgroup analysis, metoclopramide did improve endoscopic visualization among patients with acute UGIB due to gastric lesions; this was achieved through improved visualization of the fundus. Metoclopramide also reduced the need for a second look endoscopy within 72 hours.

Metoclopramide did not provide much clinical benefit in terms of EGD duration, immediate hemostasis success rate, length of hospital stay, and 30 day rebleeding rate.

Caution

There are some limitations worth noting from this trial. First, the metoclo-

pramide group had a lower hemoglobin level compared to placebo, suggesting a higher volume of blood loss in this group, which may have impacted the results. Second, metoclopramide improved visualization in the stomach from gastric lesions and reduced the need for a second look endoscopy within 72 hours; however, this trial was not adequately powered to evaluate these outcomes. Lastly, the study was conducted in 2 hospitals in Thailand, which limits the generalizability.

My Practice

I typically use prokinetic agents, either IV erythromycin 250 mg or IV metoclopramide 10 mg, for selected individuals with evidence of active upper GI bleeding or blood in the stomach such as hematemesis, coffee ground emesis, or a bloody nasogastric aspirate. The hope is that these prokinetic agents can help improve gastric visualization at the time of endoscopy by clearing the stomach of blood, clots, and food residue. I typically order these prokinetic agents to be administered intravenously 30 to 60 minutes prior to endoscopy. In determining which prokinetic agent to use, it's mainly dependent on what is available at our medical center. However, most of the times, I'm mainly using erythromycin based on a meta-analysis of nearly 600 patients and 8 studies suggesting that giving erythromycin prior to the EGD results in decreasing the need for repeat EGD because of improved visualization.[5] With the results from Vimonsuntirungsri et al.,[4] there is now additional evidence, albeit from subgroup analyses, to support metoclopramide use prior to endoscopy for an acute UGIB, especially if I suspect the bleeding source is from the stomach. In addition to prokinetic agents, I will occasionally reposition the patient from the standard left later decubitus position to the left lateral "semi-recumbent" position with the head of the bed raised. This approach can also help clear blood, clots, or debris in the fundus.

For Future Research

Future studies should compare the effectiveness between metoclopramide versus erythromycin for improving gastric visualization among patients with acute active upper GI bleeding.

Conflict of Interest

Dr. Lee reports no potential conflict of interest.

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EVIDENCE-BASED GI
AN ACG PUBLICATION

When to Discontinue Colon Polyp Surveillance in Older Adults?

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This summary reviews Lee JK, Roy A, Jensen CD, et al. Surveillance colonoscopy findings in older adults with a history of colorectal adenomas. JAMA Network Open 2024;7(4):e244611 .

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Keywords: colonoscopy, surveillance, aging, geriatrics

STRUCTURED ABSTRACT

Question: What are the rates of colorectal cancer (CRC) and advanced adenomas in older patients with prior adenomas on last colonoscopy, stratified by age and presence of non-advanced or advanced adenoma on last colonoscopy?

Design: Retrospective, population-based, cross-sectional study

Setting: Kaiser Permanente Northern California, a large community-based health system.

Patients: Patients aged 70 to 85 years old between January 1, 2017 to December 31, 2019 who had a history of adenomas detected over 12 months prior and were undergoing colonoscopy for colon polyp surveillance during the study period. Higher risk individuals with prior CRC, hereditary CRC syndrome, inflammatory bowel disease, and prior colectomy were excluded along with individuals who had colonoscopies with inadequate quality.

Interventions: Surveillance colonoscopy.

Outcomes: Rates of CRC and advanced adenoma, defined as villous adenoma, adenoma with high grade dysplasia, and adenoma $\geq$10 mm on surveillance

colonoscopy were recorded with results stratified based on age group (70-74, 75-79 or 80-85 years old) at time of surveillance colonoscopy and whether patient had non-advanced or advanced adenoma on last colonoscopy. Secondary outcomes were factors, including advancing age, body mass index (BMI), smoking history, that were associated with advanced neoplasia (advanced adenoma plus CRC).

Data Extraction and Analysis: Using the endoscopic, histologic, and demographic databases contained within Kaiser Permanente Northern California system, baseline data about prior and current colonoscopies was obtained along with demographic data. Chi-square test was performed to compare rates between groups. Multivariable logistic regression was also performed using a combination of demographic factors (gender, smoking history, BMI, etc.) to identify risk factors for advanced adenomas on surveillance colonoscopy.

Funding: The National Cancer Institute.

Results: Of 9,740 surveillance colonoscopies in 9,601 patients, 58.9%, 33.1% and 8.0% were performed in 70-74, 75-79 and 80-85 year-olds, respectively. Other demographic data included 61% male; 30% with BMI $\geq$ 30; 50% never smoked tobacco; 76% had non-advanced adenomas on index colonoscopy with mean 5.1 years between colonoscopies while 24% had advanced adenomas at index colonoscopy with mean 3.3 years between colonoscopies.

Overall, 0.3% had findings of CRC, 11.7% advanced adenoma, and 12.0% advanced neoplasia. There were no differences between age groups. CRC (0.5% vs 0.2%, $P = 0.02$) and advanced neoplasia (16.5% vs 10.6%, $P < 0.001$) were higher with prior advanced vs non-advanced adenomas. Significant adjusted covariate factors for advanced neoplasia were prior advanced adenoma (adjusted odds ratio [aOR] 1.65, 95% confidence interval [CI] 1.44-1.88), BMI $\geq$ 30 vs < 25 (aOR 1.21, 95% CI 1.03-1.44), tobacco use (aOR 1.14, 95% CI 1.01-1.30). Asian/Pacific Islanders were at lower risk (aOR 0.81, 95% CI 0.67-0.99)

COMMENTARY

Why Is This Important?

Colonoscopies in elderly patients have increased risk of complications, and gastroenterologists have to weigh this risk against the diagnostic/therapeutic benefits of colonoscopy. There is inadequate existing evidence guiding how to approach surveillance colonoscopies (i.e., when to stop colonoscopies) among older adults with prior adenoma, particularly among those with prior non-advanced adenomas (who can go 10 years between colonoscopies based on revised guidelines) vs those with prior

advanced polyps given their elevated subsequent CRC risk.[1-4]

Key Study Findings

Overall, the rate of CRC on surveillance colonoscopy in individuals ≥70 years old with non-advanced adenomas on prior colonoscopy was 0.2% with 10.4% having advanced adenomas. Considering that it takes multiple years for an advanced adenoma to develop into CRC, the yield of surveillance colonoscopy to prevent CRC in patients with history of non-advanced adenomas seems low.

Among other factors predictive of advanced neoplasia at surveillance colonoscopy, prior advanced adenoma (aOR 1.65, 95% CI 1.44-1.88) was the only factor that was associated with a clinically important increase in risk.

Given that life-table analysis demonstrate limited life expectancy for individuals ≥70 years old, especially if the individual has a history of cardiovascular disease, diabetes, or tobacco use, the benefit of surveillance colonoscopy if the patient has non-advanced adenomas on index colonoscopy is probably quite limited.

Caution

First, remember that this study does not address at what age we should no longer offer index (first-time) CRC screening.[5] Second, while the rate of CRC was low, a fair proportion of patients with prior advanced adenomas did have metachronous advanced colorectal polyps. While these are still "pre-cancerous," it is difficult to discern whether these patients were at particularly high risk of future CRC risk for a longer follow-up period thereafter. Third, the study did not have enough granularity of data to discern details of family history of CRC (who was affected and at what age), as a first-degree family member with early onset CRC increases familial risk of CRC much more than a second-degree family member with later onset CRC.

My Practice

In older patients ≥ 70 years old with prior non-advanced adenomas, I tend to encourage cessation or limitation of future colonoscopies. This does not preclude future onset of CRC, but it is important to discuss with the patient that performing colonoscopy at an elderly age may not be worth the burden of bowel preparation or procedural risk compared to a low future CRC risk. In similar patients with prior advanced adenomas, I may discuss 1-2 further colonoscopies depending on their overall health and personal preference. In my practice population, we have a fair number of otherwise healthy patients who have undergone colectomies for CRC well into their 80s or even 90s without major complications.

For Future Research

While this study can aid us in shared decision-making regarding cessation of colonoscopy in older patients with prior

adenomas overall, future studies that attempt to differentiate risk based on type of previous advanced polyps (i.e., based on size alone, or advanced histology such as high grade dysplasia) would assist in targeting those who may be at particularly higher risk of future CRC. Future research regarding cessation of colonoscopy in those with prior CRC may also similarly assist in determining cessation of surveillance colonoscopies.

Conflict of Interest

Dr Yen has no conflicts of interest.

Note: The authors of this study are active on social media. Tag them to discuss their work and this EBGI summary.

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