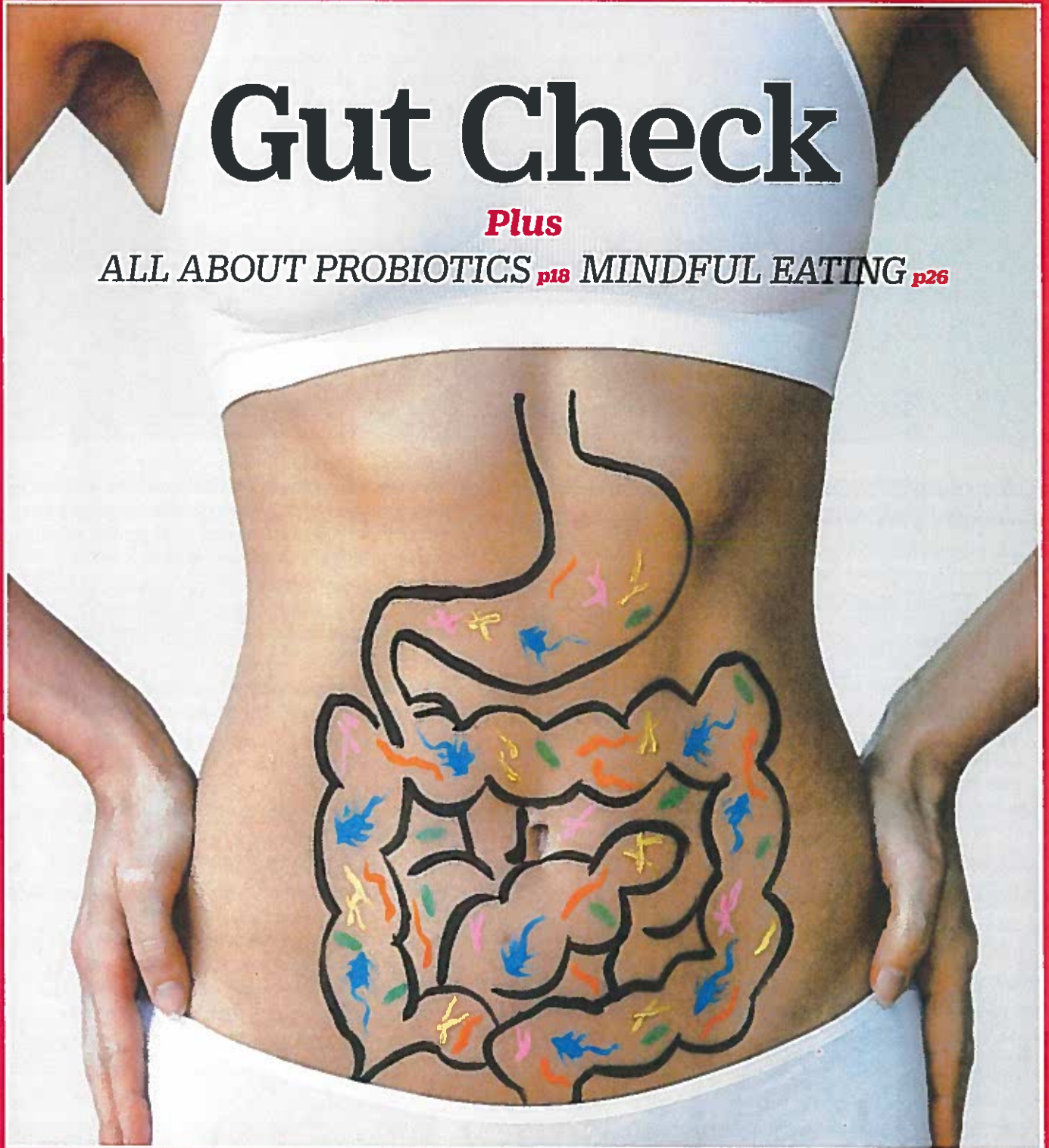


# TIME HEALTH TIME

## Gut Check

Plus

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# The Rewards And Risks of Probiotics

THE PRELIMINARY STUDIES WERE ENCOURAGING, AND researchers were hopeful. Among kids with acute gastroenteritis—a type of inflammatory gut infection, and a leading cause of death among children worldwide—a daily course of probiotics, coupled with standard therapy, had outperformed placebos in treating the worst of the kids' gastrointestinal (GI) symptoms.

Those early findings led to a nationwide study involving dozens of U.S. universities and more than 900 children suffering from acute gastroenteritis. But this time, the results, published late last year in the *New England Journal of Medicine*, were disappointing. Kids who received a five-day course of *Lactobacillus rhamnosus GG*—one of the most popular and widely administered species of probiotic bacteria—did not fare any better than kids who got a placebo.

"The rigor of our research design calls into question recommendations to use *L. rhamnosus GG*," the authors of that study wrote. Their conclusion—like those of many of the most recent and comprehensive clinical trials on probiotics for the treatment of inflammatory gut conditions—is not that probiotics are ineffective. Instead, they wrote, "responsiveness to probiotics may follow highly individualized patterns."

In other words, how a person responds to a probiotic likely depends on the unique ecosystem of gut bacteria that live within that individual. The question, then, is less how you treat colitis and other inflammatory gut conditions with probiotics; it's how you treat them in any particular person with any particular gut ecology—especially since the very process of probiotic therapy involves introducing still more bacteria or yeast into that already complicated mix. The challenges suggest

themselves: try to understand the behavior of any random million people. Then try to predict how it will change when you add a few tens of thousands more. Good luck with that.

"The simple explanation for how probiotics work"—and the one most people have absorbed from media reports and product-marketing campaigns—"is that the bacteria in our guts exists in this yin and yang of good and bad," says Dr. Raymond Cross, a professor of medicine and director of the Inflammatory Bowel Disease Program at the University of Maryland Medical Center. "By taking probiotics, the thought is that we're increasing the good bacteria, which should provide a benefit."

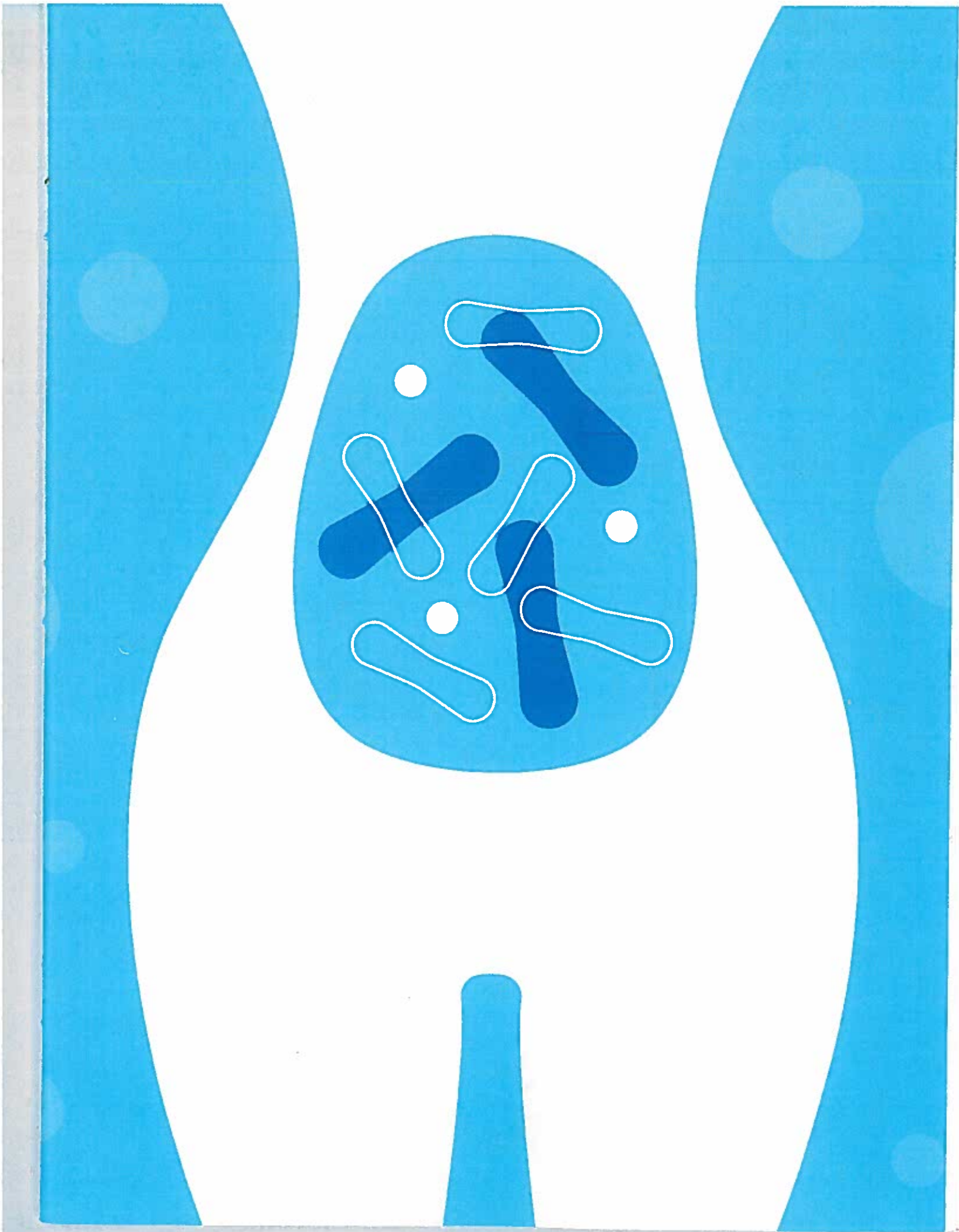
But the gut's microbiome is not so easy to war-game. "The effectiveness of a probiotic probably depends on the types of bacteria we need, how much of them we need and how often we need to take them, but these are all things we don't know now," Cross says. The right answer to each of those questions varies from one person to the next. On top of that, he says, "We don't even really know exactly how probiotics work."

While it's possible that ingesting probiotic bacteria changes the composition of a person's gut microbiome, probiotics might also work in other ways, says Dr. Berkeley Limketkai, director of clinical research at the UCLA Center for Inflammatory Bowel Diseases. "It may not be the microbes themselves that provide a health benefit, but the substances they produce," he says.

The microbes in the gut process a lot of things a person ingests. "And there's increasing investigation into the idea that when you ingest probiotics, the existing microbes break down the probiotics into by-products that get into the blood and produce effects," he explains. These by-products, known as metabolites, could work by suppressing the gut's secretion of

Why cautious experimentation along with traditional treatment is best for people with ulcerative colitis

By Markham Heid



pro-inflammatory molecules, or they could increase the secretion of anti-inflammatory gut chemicals. Or both.

While there are many unanswered questions, gut experts say plenty of research does suggest that probiotics can help people with ulcerative colitis. "There are some studies on various probiotic formulations showing that they may be able to prevent relapse and may be useful as an add-on therapy," Cross says. One example, he says, is a commercially available probiotic cocktail called VSL#3, which contains a mixture of four strains of *Lactobacillus*, three of *Bifidobacteria* and the strain *Streptococcus thermophilus*.

A small 2009 study, published in the journal *Clinical Gastroenterology and Hepatology* found that people with mild or moderate ulcerative colitis who took VSL#3 twice a day for 12 weeks experienced a larger reduction in their symptoms than those who took a placebo. Some other studies—in both animals and people—have also found evidence that VSL#3 may be effective in the treatment of ulcerative colitis. Other GI doctors also mention VSL#3 when asked which of the current batch of probiotics has the most evidence backing it up.

But again, the picture is complicated. The company that produces VSL#3 has been in legal disputes with the scientist who developed it. That scientist claims that his original and evidence-backed VSL#3 mixture has been altered, and he's now selling a product called Visbiome, which he says is the true and research-vetted probiotic formulation.

Cross says both products are among the handful he'll sign off on for his ulcerative colitis patients. (Other products he'll greenlight include Align and Culturelle.) But he says he okays these probiotics mostly because they seem to be safe and many patients tell him they want to give probiotics a try—not because he's certain they'll help.

"These are the brands I know and that have been around for a while, and that have some studies to support them," he says.

But, he cautions, determining which may work best for a patient is at this point an open question.

Other experts voice a similar mixture of enthusiasm and trepidation. "It's difficult topic if you want hard answers," says Dr. Emeran Mayer, a professor of medicine and co-director of the Digestive Diseases Research Center at UCLA. He says that in studies using mice, probiotics have "fairly consistently" produced benefits in immune-system activity, gut permeability and the duration of ulcerative colitis symptoms. "But things always seem to work better in mouse models," he says. "If you go to humans and high-quality studies, you don't see this consistent effect."

Mayer echoes that one of the challenges of treating colitis patients with the current crop of probiotic products is that by and large, these aren't single formulations that work on all people—and he backs that up with some details on just how varied our guts are. "If you look at the relative abundance of microbial strains in the human gut, any one person only shares about 10% with anyone else," he says. "So there's this huge diversity from one person to the next, and the approach of using the same probiotic strain or mixture of strains to treat people with different microbial and metabolic profiles only works for a portion of people." This helps explain why a lot of the studies on probiotics in people have produced uninspiring results.

Not only have some of these human trials failed to replicate the benefits observed in animal studies, but some of the latest research has turned up evidence of potential harm. A 2018 study in the journal *Cell* found that a particular mixture of probiotics seemed to interfere with the repopulation of healthy gut bacteria among people who had recently been on antibiotics. "The dogma had always been that probiotics speed up recolonization of the microbiome, but [this study] actually showed the opposite," Mayer says. "For the first time, we're starting to talk about the potential negative effects of probiotics."



**'In general, I think probiotics are fairly benign, but one could theoretically overdose or end up with a result that's less favorable.'**

—Dr. Berkeley Limketkai, director of clinical research at the UCLA Center for Inflammatory Bowel Diseases

## Sources of probiotics



Another study, from the University of Texas MD Anderson Cancer Center, found that probiotics may decrease the effectiveness of immunotherapy among those with melanoma. “People say, ‘What do you mean? I thought probiotics were good for you.’” says Lorenzo Cohen, one of the authors of the study and director of the Integrative Medicine Program at MD Anderson in Houston. “But by taking a probiotic supplement you may be overcrowding the gut with very few strains all from the same family.” This may lead to a drop in microbiome diversity, he adds, which is a bad thing.

While those studies did not involve people with ulcerative colitis, they still illustrate the changing thinking and potential risk associated with probiotics. When it comes to ulcerative colitis, specifically, experts say negative side effects are rare—but they do turn up. “I’ve had patients whose diarrhea got worse or had bloating or abdominal pain after taking probiotics,” Limketkai says. “In general, I think probiotics are fairly benign, but one could theoretically overdose or end up with a result that’s less favorable.”

Adds Mayer: “I would say yes, there’s a potential risk, but if you look at the millions of people who are taking probiotics, there’s never been a signal that people consistently got worse.” The bulk of the evidence to date suggests the available probiotic products are more likely to be either helpful or harmless, he says.

In the future, both the rewards and the risks of probiotics may increase. “I think that five years from now, we’ll have

personalized prescription of designer probiotics,” Mayer says. Using genetic testing and other tools, doctors should soon be able to map the makeup of a person’s microbiome and offer probiotic cocktails tailored to their gut, he explains. This should lead to more reliable benefits.

At the same time, Mayer says he worries about certain synthetic probiotics, some of which may hit the marketplace in the not-too-distant future. “I think that with these novel, genetically engineered probiotics, the danger of unanticipated side effects will be much higher,” he says. The human microbiome is an incredibly complex ecosystem, he explains, and adding something new to it could have serious and unexpected consequences. “If you add in an organism, it may have a huge effect or it may have no effect whatsoever, and that effect could be good or bad,” he says.

Asked how ulcerative colitis patients should approach the use of probiotics, experts recommend cautious experimentation alongside traditional treatment methods. “If a patient asks, I often tell them to take a product that contains a minimum of 450 billion bacteria, either all at once or broken up into two daily doses,” Limketkai says. While that may sound like a lot, he says some products contain nearly 2 trillion bacteria. He also suggests probiotics that contain several strains—instead of a whopping dose of a single bacterium.

If the probiotic you’re using causes any problems, stop taking it.

At the same time, he and other experts say people with ulcerative colitis who take probiotics shouldn’t stop taking their prescription medications. “People want to find nondrug treatment options, and some turn to probiotics, but I don’t recommend them as monotherapy because their benefits are inconsistent,” Limketkai says. Cross agrees. “I tell my patients the most important thing is that you come back for all your appointments and that you take your medication 80% of the time or more,” he says.

Mayer, meanwhile, says eating fermented foods that contain probiotics may be a safer, healthier route than taking supplements. “From Turkey to Asia, people have been eating probiotic foods for health for hundreds and thousands of years,” he says. He mentions kefir, kombucha, sauerkraut, yogurt and kimchi as examples of probiotic foods. “More than half the world’s population eats significant amounts of these foods, so there’s no question that they’re safe, and they may provide benefits,” he adds.

It’s even possible that eating some nonprobiotic foods may promote healthy microbiome changes. MD Anderson’s Cohen says diets high in fiber seem to promote healthy gut function. And several studies have linked high-fiber diets to improvements among people with inflammatory bowel disease.

Like so many popular medical options, probiotics hold an immense amount of promise for people with ulcerative colitis. But as of today, much of that promise has yet to be realized. □