Clinical trial: Fecal matter transplant helps half of patients with GI cancers overcome immunotherapy resistance

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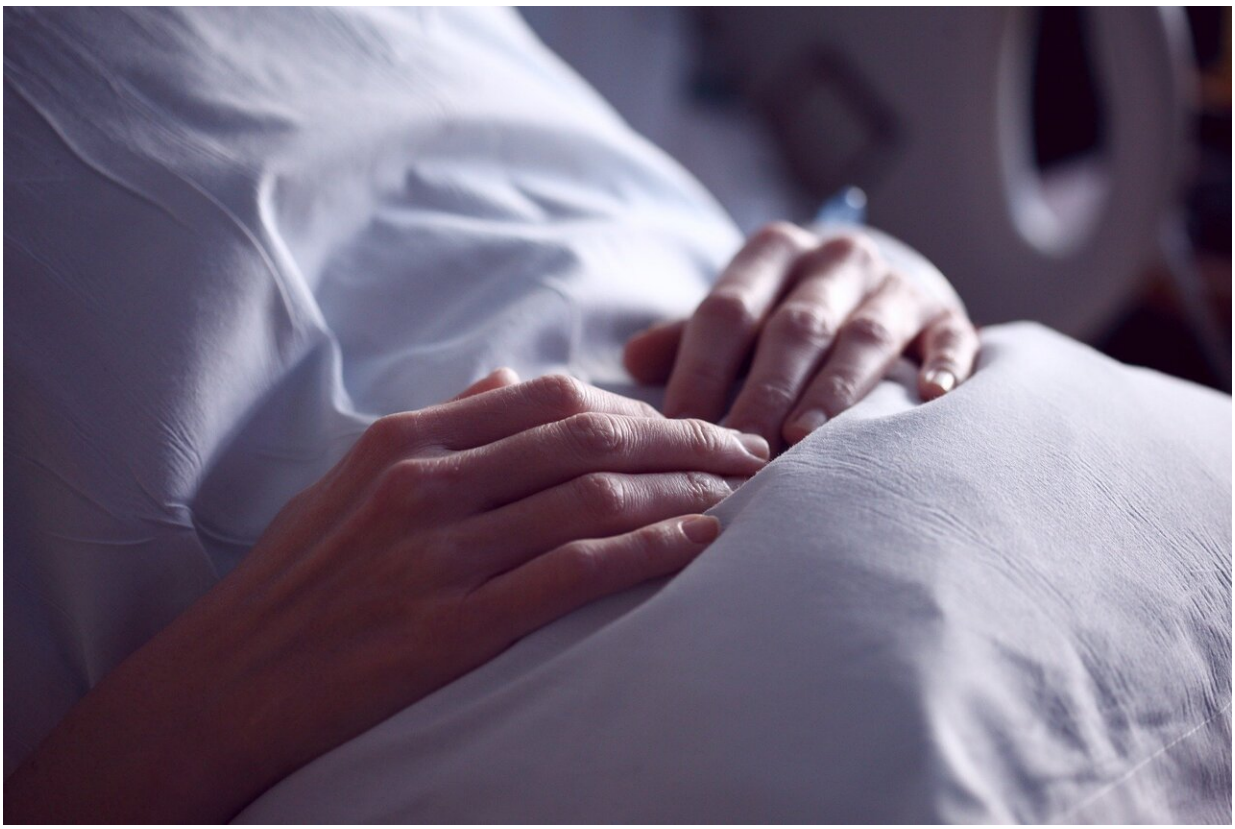

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Findings from a small, proof-of-concept clinical trial have suggested that fecal microbiota transplants (FMTs) can boost the effectiveness of

immunotherapy in a range of gastrointestinal cancers.

In the study, published July 25 in the journal *Cell Host & Microbe*, six of 13 patients who had previously shown resistance to immune checkpoint inhibitors benefited from receiving FMTs from donors who had previously responded to treatment. The investigators also identified specific strains of bacteria associated with better or worse responses to FMT and immune checkpoint drugs.

"This research highlights the complex interplay between beneficial and detrimental bacteria within the gut microbiota in determining treatment outcomes," says co-corresponding author Hansoo Park of Gwangju Institute of Science and Technology, in Gwangju, South Korea.

"While the connection between gut microbiota and immune response to cancer therapy has been a growing area of interest, our study provides concrete evidence and new avenues for improving treatment outcomes in a broader range of cancers."

Immune checkpoint inhibitors have revolutionized cancer treatment, but many patients never respond or develop resistance after an initial response. The researchers decided to study FMT in patients receiving immune checkpoint inhibitors because emerging evidence suggests that the gut microbiota plays a crucial role in modulating the immune system and can significantly impact the efficacy of these therapies.

Previous small clinical trials had reported that FMTs could overcome resistance to immune checkpoint inhibitors in some melanoma patients, but the potential for FMTs to overcome resistance in other advanced solid cancers had not been explored.

This study is the first to show the potential benefits of this treatment in clinical settings beyond melanoma.

The trial included patients with metastatic solid-tumor cancers who were resistant to the anti-PD-1 drug nivolumab. Four had gastric cancer, five had esophageal cancer, and four had hepatocellular carcinoma.

The six FMT donors, who also had gastric cancer, esophageal cancer, or hepatocellular carcinoma, had had a complete or partial response for at least six months after treatment with nivolumab or pembrolizumab. The FMTs were given via colonoscopy after the recipients had received antibiotics to tamp down their own microbiotas.

"One of the most surprising results was from a hepatocellular carcinoma patient who initially showed no response to the first FMT and continued to experience cancer progression. However, after switching the donor for the second FMT, the patient exhibited remarkable tumor shrinkage," says co-corresponding author Sook Ryun Park, of Asan Medical Center at the University of Ulsan College of Medicine in Seoul, South Korea.

"Both donors were long-lasting, good responders to anti-PD-1 inhibitors, but because we did not yet know the causative bacteria responsible for the FMT response, we could not predict whether the treatment would be effective."

The investigators then took a closer look at which bacteria were most likely to affect whether patients benefited from FMT combined with checkpoint inhibitors. In doing so, they identified a novel bacterial strain that helped to improve FMT efficacy, Prevotella merdae Immunoactis.

They also identified two strains that had a detrimental impact on FMT efficacy, Lactobacillus salivarius and Bacteroides plebeius.

They plan to continue studying these and other strains with the goal of developing better ways to boost immunotherapy effectiveness by altering the gut microbiota.

"By examining the complex interactions within the microbiome, we hope to identify optimal microbial communities that can be used to enhance cancer treatment outcomes," says Hansoo Park.

"This comprehensive approach will help us understand how the microbial ecosystem as a whole contributes to therapeutic success."

The researchers acknowledge the challenges of adopting FMT as part of standard treatment on a broad scale, including the lack of standardized protocols and regulatory guidelines, the potential risks of transmitting pathogens, and logistical issues surrounding large-scale manufacturing and distribution of FMT products.

"Developing efficient and cost-effective methods for production and distribution is necessary for widespread adoption," says Sook Ryun Park. "Addressing these challenges through comprehensive research and careful planning will be essential for integrating FMT into the standard of care for cancer treatment."

More information: Fecal microbiota transplantation improves anti-PD-1 inhibitor efficacy in refractory unresectable or metastatic solid cancers refractory to anti-PD-1 inhibitor, *Cell Host & Microbe* (2024). DOI: 10.1016/j.chom.2024.06.010. www.cell.com/cell-host-microbe … 1931-3128(24)00228-2

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