

Gut Instincts

Mapping the Intestinal Microbiome for Clues About Cancer

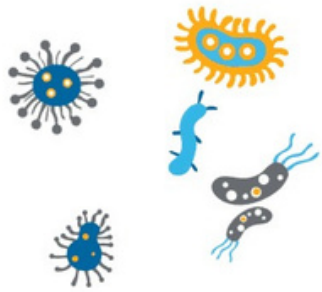
July 02, 2021

Shuji Ogino
Immunotherapy
Rectal Cancer
Colon Cancer

By Robert Levy

It's a jungle in there. The human colon, or large intestine, is home to one of the densest, most diverse collections of microorganisms on the planet. Consisting of trillions of bacteria cells in hundreds of species, along with untold numbers of viruses, parasites, and fungi, this wee wildlife, collectively known as the intestinal microbiome, are involved in everything from digesting food to regulating the immune system.

The possibility that the microbiome plays a role in colon cancer — as either a promoter or inhibitor — has fascinated scientists for years. Cancer is notorious for altering its environment to suit its needs: coaxing other cells to soften up nearby tissue so tumor cells can slip through, for example, or pacifying immune system cells that normally would attack a tumor. It would be very un-cancer-like for colon tumors *not* to try to make use of the bacterial and microbial riches in their vicinity. It would be equally surprising if at least some of those microbes — so various in their functions and behavior — didn't exert a restraining force on cancer.



Research into the relationship of colon cancer and the microbiome has boomed in recent years as technology has enabled investigators to survey the occupants of the colon with unprecedented precision and scientists have gained a deeper understanding of the microbiome's role in overall health. Once viewed primarily as a workforce for breaking down fiber and certain carbohydrates in food and producing substances like vitamins B_{12} and K, gut bacteria also stop harmful bacteria from overrunning the intestine, prevent certain allergies, and even communicate with the brain.

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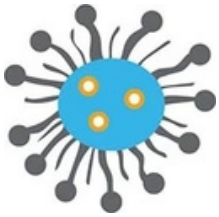
Wendy Garrett, MD, PhD



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"The totality of the implications of the microbiome for cancer is grand — from prevention to treatment — and as such we have a grand challenge before us," says Wendy Garrett, MD, PhD, of Dana-Farber's Center for Gastrointestinal Oncology and of the Harvard T.H. Chan School of Public Health and co-director of the Harvard Chan Microbiome Public Health Center, whose research focuses on the interactions between microbes and their hosts and how those interactions may affect inflammatory bowel diseases and cancer.

The study of the relationship between the intestinal microbiome and cancer received a powerful push in 2019 with the awarding of a $25 million Grand Challenge grant from Cancer Research UK, a charity based in the United Kingdom, to an international team of 14 scientists. The program's focus is explicit in its name: Opportunity to Investigate the Microbiome's Impact on Science and Treatment In Colorectal Cancer, or OPTIMISTICC. Its goal is ambitious: to pinpoint how the microbiome impacts the onset and development of colorectal cancer and to use those findings to improve outcomes for people with the disease. Its leaders are Garrett and Matthew Meyerson, MD, PhD, director of Dana-Farber's Center for Cancer Genomics.



The program brings together the elements — data, tissue samples, and scientific talent — needed for a sustained assault on the question of whether the microbiome impacts cancer and, if it does, how that relationship can be manipulated to help patients.

"We have computational biologists, cancer genomicists, clinical trial leaders in colon cancer, epidemiologists, immunologists, and microbiologists on a dream team that can focus like a laser on colon cancer and the microbiome," Garrett says. "It's a thrilling and transformative opportunity for microbiome science and for our patients."

The program's clinical flagship study, known as MICROCOSM (for MICRObiome of Colorectal Cancer: Longitudinal Study of Mechanism), is collecting long-term health information and tissue and stool samples from more than 2,500 people across North America and Europe who were being treated for colorectal cancer. Researchers are not only exploring whether the microbiome plays a role in the formation or growth of colorectal cancer but also whether it has an impact, positively or negatively, on the effectiveness of treatment and the side effects of various therapies.

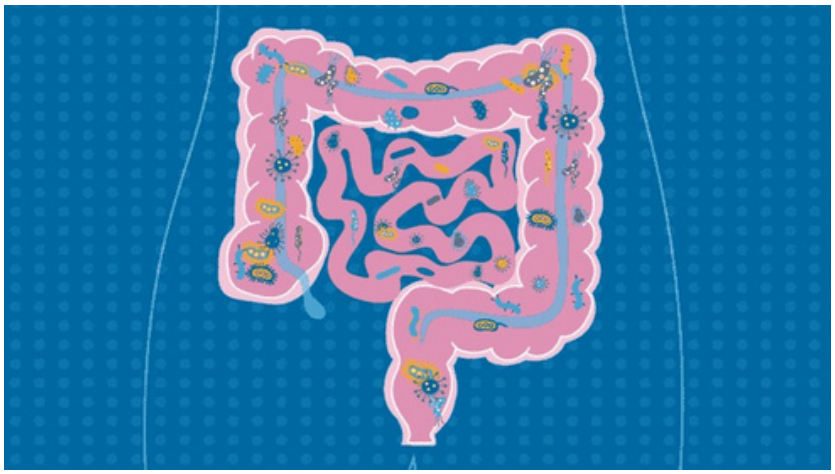


Kimmie Ng, MD, MPH

"With MICROCOSM, we established an infrastructure to collect these samples and generate data from them — on the genetic makeup of the tumor cells and bacteria cells, on the type of immune system cells mixed in with them — and really begin to crack whether there's a link between the microbes that live in a person's gut, in their tumor, and their response to treatment," says Kimmie Ng, MD, MPH, co-director of the Colon and Rectal Cancer Center and director of the Young-Onset Colorectal Cancer Center at Dana-Farber, as well as a member of the OPTIMISTICC team that is co-leading MICROCOSM. "And layered on top of that, we'll have data on everything from where participants live to what they eat to how much they exercise, which will help us answer a wide range of questions about how environmental factors shape the microbiome and influence treatment response."

New Tools to Identify Intestinal Microbes

Though scientists have speculated about a link between the microbiome and colon cancer for ages, it is only relatively recently that technology has handed them the tools needed to obtain a definitive answer. A key advance was Meyerson's development in the early 2000s of a method called sequence-based computational subtraction. Though its name is a mouthful, the concept is simple: collect a stool sample from an individual, sequence the DNA of all the cells within it, and subtract out the human DNA. What's left is the DNA of intestinal microbes — bacteria, viruses, fungi, and parasites.





Matthew Meyerson, MD, PhD

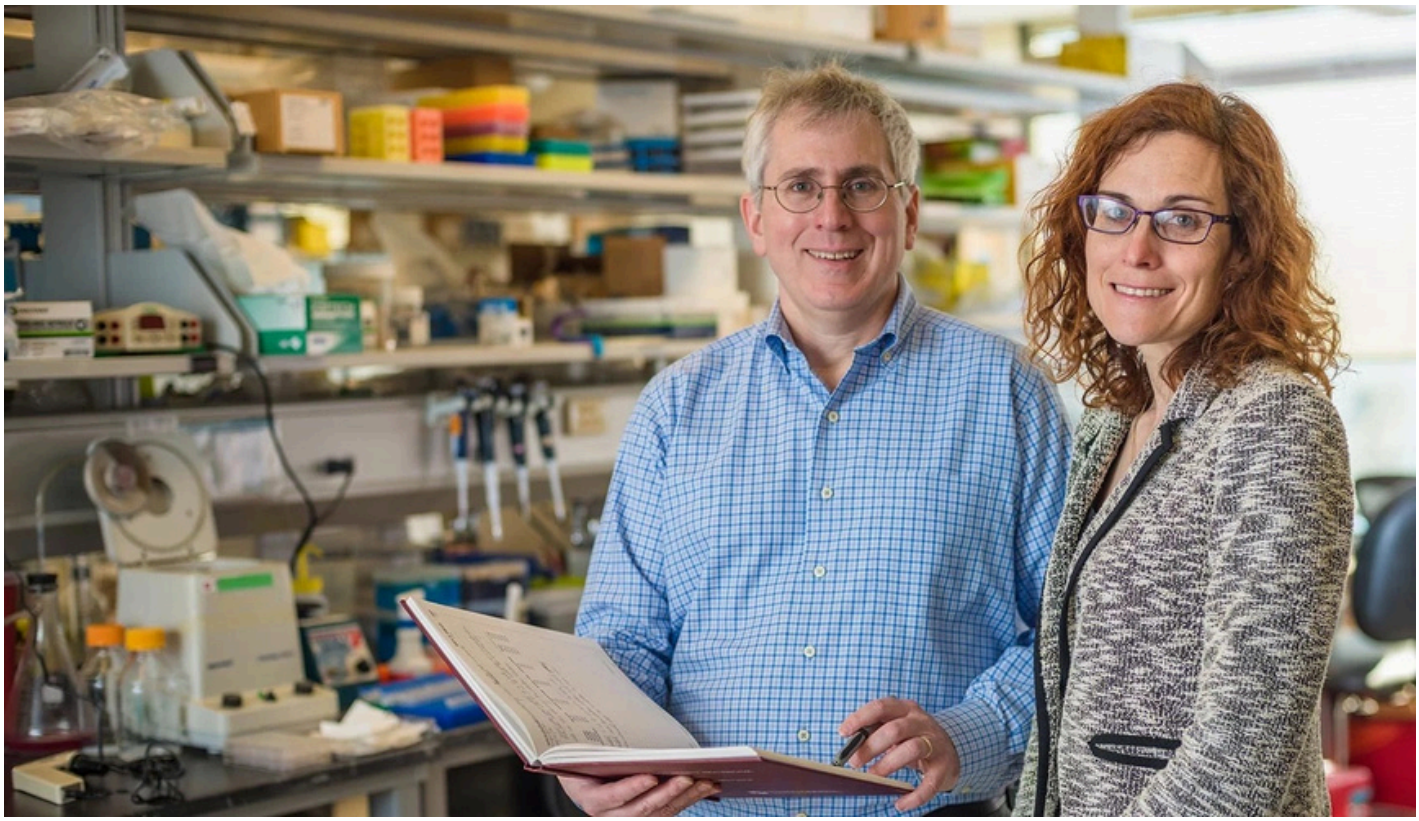
The approach was powerful in principle, but the DNA-sequencing technology of the time didn't have the capacity to process large-enough numbers of cells. About a decade later, Aleksandar Kostic, a PhD student in Meyerson's lab (and now a researcher at Joslin Diabetes Center), created a more powerful system, called PathSeq, that uses next-generation sequencing. With it, he analyzed colon cancer samples to see what types of bacteria were present.

In a study published in 2011, Meyerson, Garrett, Kostic, and colleagues at Dana-Farber and the Broad Institute of MIT and Harvard reported that they'd found strikingly high levels of the bacterium *Fusobacterium nucleatum* in colorectal cancers. What made the discovery particularly notable was that *Fusobacterium* is usually found in the mouth, not the bowel.



The study was followed by another, by Meyerson, Garrett, and Marios Giannakis, MD, PhD, of Dana-Farber, and Shuji Ogino, MD, PhD, now at Brigham and Women's Hospital, that indicated that patients whose colorectal tumors harbored high levels of *Fusobacterium* had worse prognoses than those whose tumors had lower levels of the bug. A 2017 study led by Meyerson and co-authored by Ng and Giannakis found that when colorectal cancer cells metastasize to other parts of the body, the roving cells brought along some of their bacterial cronies from the colon, including *Fusobacterium nucleatum*, like mementos from home. In studies with animal models carrying the metastatic cells, the researchers found that treating the animals with an antibiotic that targets many bacteria, including *Fusobacterium*, caused tumor cell proliferation to decline.

Findings like these point to an association between certain gut bacteria and tumors of the colon. But as scientists are quick to point out, association is not causation. As Meyerson puts it, "What we don't know yet is do these bacteria actually provoke the growth of the cancer or are they merely opportunistic: are they there primarily because the cancer provides a good environment for them? Or is it some combination of the two? Despite a lot of research in the field, we really don't have a clear answer to that question."



Matthew Meyerson, MD, PhD, and Wendy Garrett, MD, PhD

Seeking the Cancer-Microbiome Link

To truly make the case that the microbiome has an impact on colorectal cancer or the effectiveness of therapies, it would be necessary to find a mechanistic connection — a chain of interactions by which gut microbes alter the behavior of tumor cells and the immune cells in their vicinity. Both Garrett and Giannakis, who is also a member of the OPTIMISTICC team, are at the forefront of these efforts.

In her lab at the Harvard T.H. Chan School, Garrett is probing the microbiome/colon cancer nexus with the biological equivalent of a clean slate. Working with "gnotobiotic" mouse models — animals that are utterly microbe-free — Garrett and her colleagues are implanting the animals with specific sets of intestinal microbes to identify which of them, if any, have an effect on colon cancer.

"We've studied *Fusobacterium* and how it might influence the immune system in creating conditions that promote cancer in the colon," Garrett remarks. "We've studied not only fusobacterial metabolic products to see how they contribute to colon cancer, but also microbial metabolites that hinder colon cancer development. We're very interested in diet at the molecular level. With Dr. Kimmie Ng and her group, we're working to identify associations between dietary micronutrients and the microbiome in the colon. The goal is to pull apart their mechanistic links using tools like gnotobiotics to develop microbiome-targeted therapies that we can bring back to patients."



Faecalibacterium prausnitzii bacteria (shown above) is one of the most abundant bacterial species found in the human gut. Its presence is thought to give protection against a number of gut disorders including inflammatory bowel disease, Crohn's disease, and colon cancer.

One area of interest underscores just how much remains to be learned about the microbiome: where, in relation to all the other cells in the intestinal environment is the microbiome located and how does it interact with neighboring cells? To find out, Giannakis and his colleagues are studying colorectal tumors at the single-cell level to produce an "atlas" of the disease. They're also developing three-dimensional laboratory models of colorectal cancer in hopes of simulating the conditions of the colon and its environment. The models, which include immune system cells, stromal cells like those found in connective tissue, along with normal and colon cancer cells, enable scientists to zoom in on the interactions between specific cell types.

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Marios Giannakis, MD, PhD

"We're particularly interested in finding ways to improve the effectiveness of immunotherapy in colon cancer," Giannakis says. Immunotherapies have been less successful against colorectal cancer than other forms of cancer. "Does the microbiome affect the immune system in ways that hamper immune-stimulating therapies?" Giannakis asks. "If that's the case, can we modify the microbiome to reap the benefits of these treatments?"



Marios Giannakis, MD, PhD



He acknowledges that microbiome research is still in its infancy and that much remains to be discovered. "We're still very much in the descriptive stage," he says. "In many ways the intestine is terra incognita. We're trying to find out what species are there, in what proportions, and who they cohabitate with."

But if researchers uncover a definitive connection between the microbiome and colon cancer, the consequences for prevention and treatment of the disease could be profound.

"If we find a unique microbial signature in people who later develop colon cancer, we could potentially create a screening or early-detection test that would be a lot less invasive than current techniques," Ng comments. "If we can nail down what the predictors of treatment response are, we may be in a position to alter the microbiome to produce better results for patients."