OncoLog
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RAS Mutations and Colorectal Cancer Liver Metastases

Gene mutations may have implications for local therapy for liver metastases from colorectal cancer

By Joe Munch

Mutations of the *RAS* oncogene are known to predict poor overall and recurrence-free survival for patients who receive systemic therapy for colorectal cancer liver metastases. Now, the findings of recent studies from The University of Texas MD Anderson Cancer Center suggest that *RAS* mutations affect the outcome of local therapy for these metastases.

"This goes beyond just predicting survival," said Jean-Nicolas Vauthey, M.D., a professor and chief of the Hepato-Pancreato-Biliary Surgery Section in the Department of Surgical Oncology.

Noting that *RAS* mutations have long been known to render EGFR (epidermal growth factor receptor)-targeting therapies such as cetuximab and panitumumab ineffective, Dr. Vauthey said, "We need to understand that *RAS* mutation status has treatment implications besides targeted therapy selection. We're showing for the first time that *RAS* mutation status needs to be considered when making local treatment decisions for patients with colorectal cancer liver metastases."

A scatter plot of 25 liver metastases in 22 patients who had local tumor progression (LTP) after percutaneous ablation shows that lesions with mutant RAS *(blue crosses) had shorter times to LTP and were smaller than lesions with wild-type* RAS *(red circles).* RAS *mutations were associated with worse 3-year LTP-free survival rates in both univariable and multivariable analyses; tumor size of 2 cm or more was associated with lower 3-year LTP-free survival rates in univariable, but not multivariable, analysis (data not shown). Image used with permission from* Br J Surg, *2017;104:760–768.*

Implications for surgery

For many patients who have colorectal cancer liver metastases and either no evidence of disease outside the liver or extrahepatic disease considered to be completely resectable, neoadjuvant chemotherapy followed by hepatectomy offers the best chance at a cure. Whether such surgery is successful is determined in part by assessing the surgical margins surrounding the resected tumors—negative margins indicate success, whereas positive margins indicate an increased risk for recurrence.

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RAS Mutations and Colorectal Cancer Liver Metastases

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patients with colorectal cancer liver metastases, surgeons have traditionally aimed for gross resection margins of 10 mm. However, the findings of a recent study led by Dr. Vauthey may change this recommendation for some patients.

For their study, Dr. Vauthey and his colleagues reviewed the cases of 633 patients who underwent potentially curative resection of colorectal cancer liver metastases using traditional 10-mm resection margins. *RAS* mutations were found in metastatic tumors removed from 229 of these patients.

Of the 633 patients, 225 developed a liver-first recurrence after resection of the liver metastases. "Among patients whose disease recurred in the liver after resection, the median tumor-free margins on pathological examination were much narrower in patients with *RAS* mutations (4 mm) than in patients without *RAS* mutations (7 mm)," Dr. Vauthey said. "We also found that patients with mutant *RAS* had more than double the rate of microscopically positive margins than patients with wild-type *RAS* did."

In fact, *RAS* mutation and carcinoembryonic antigen levels of 4.5 ng/mL or more were the only independent predictors of positive margins.

"Our findings suggest that tumors with *RAS* mutations have a different phenotype. The morphology of the tumor may be different, or there might be micrometastases around the tumor that we don't see as we're doing our resection," Dr. Vauthey said. "The practical implication of these findings is that we are now aiming for wider gross resection margins—15 mm instead of 10 mm—when we resect colorectal cancer liver metastases in patients with *RAS* mutations or unknown *RAS* status because we think it will be beneficial for the patient."

Implications for ablation

Patients who have colorectal cancer liver metastases that are not amenable to surgery or who cannot undergo surgery for other reasons may undergo image-guided percutaneous ablation of the lesions. Bruno Odisio, M.D., an assistant professor in the Department of Interventional Radiology, was the first author on a recent study to determine whether *RAS* mutations—already found to be associated with worse preoperative chemotherapy responses, worse survival outcomes, and now narrower tumor-free margins in patients with colorectal cancer liver metastases—might also be related to outcomes of liver ablation.

"Essentially, patients with *RAS* mutations have a more aggressive phenotype with a more invasive and migratory tumor biology."

– Dr. Bruno Odisio

In the study, Dr. Odisio and his colleagues (including Dr. Vauthey, the study's senior author) looked at the cases of 92 colorectal cancer patients with known *RAS* mutation status who underwent percutaneous ablation of 137 liver metastases. Three years after ablation, the rate of local tumor progression (i.e., recurrence at the ablated tumor site) in the patients whose tumors had mutant *RAS* (39%) was significantly higher than that of the patients with wild-type *RAS* (14%).

Patients with mutant *RAS* also had a significantly worse 3-year overall survival rate than patients with wild-type *RAS* did. The patients with mutant *RAS* also tended to have disease recurrence much earlier. Mutant *RAS* and an ablation margin of less than 5 mm were independent predictors of worse local tumor progression–free survival.

"Essentially, patients with *RAS* mutations have a more aggressive phenotype with a more invasive and migratory tumor biology," Dr. Odisio said. "So maybe what we're seeing on computed tomography or magnetic resonance imaging during ablation doesn't really correlate with what's happening at the microscopic level."

Their findings prompted Dr. Odisio and his colleagues to study whether enlarging the ablation area for patients with *RAS* mutations decreases recurrence. In this recently completed study, which has not yet been published, the researchers found that the rates of recurrence following percutaneous ablation of colorectal cancer liver metastases were significantly lower for tumors in which the ablation margin was 10 mm or wider than for tumors in which the ablation margin was less

"[P]atients with mutant *RAS* had more than double the rate of microscopically positive [surgical] margins."

– Dr. Jean-Nicolas Vauthey

than 10 mm. However, regardless of ablation margins, patients with *RAS* mutations had a significantly higher rate of recurrence after ablation than did those with wild-type *RAS*.

Dr. Odisio noted that the studies' findings should be interpreted with care. "The fact that a patient has mutant *RAS* doesn't mean that the patient has a contraindication to ablation. It just means that the outcomes we can expect for that patient are not going to be as good as those for a patient without the mutation," he said. "This further understanding of the patient's tumor biology helps us to have a more tailored conversation in the clinic. We shouldn't refrain from offering ablation to patients with *RAS* mutations, but—similarly to surgery—we need to aim for wider ablation margins in order to reduce the rates of local recurrence." However, Dr. Odisio added, larger ablations are not always possible in patients with large tumors near critical structures, and other treatments may be more appropriate for such patients.

Ongoing efforts

Drs. Vauthey and Odisio are spearheading other efforts to better understand the development of colorectal cancer liver metastases and improve patient outcomes. For example, Dr. Odisio is looking at the possibility of using circulating tumor DNA, which is released into the bloodstream by dying tumor cells, to determine the completeness of ablation. And Dr. Vauthey is investigating the relationship between *RAS* mutation status and micrometastasis.

"We're collecting surgical specimens to compare the rate of micrometastasis between *RAS* mutant tumors and *RAS* wild-type tumors," Dr. Vauthey said. "We're also using next-generation sequencing to study all the other mutations in colorectal cancer that might have a bearing on treatment decisions."

In the meantime, Dr. Vauthey said, "We are now in an era in which knowing the *RAS* mutation status could change the way we treat patients, and we may be able to change their outcomes by improving local therapy." ■

Dr. Jean-Nicolas Vauthey contributed to this article.

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FURTHER READING

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Active Surveillance for Prostate Cancer

Clinical trial may clarify which patients with prostate cancer will benefit from active surveillance rather than immediate treatment

By Bryan Tutt

Because prostate cancer is often indolent and its treatment can negatively affect quality of life, active surveillance is an attractive disease management option for many patients with early-stage, low-risk disease. But the optimal selection criteria for active surveillance remain undefined. An ongoing clinical trial at The University of Texas MD Anderson Cancer Center may uncover prognostic factors for disease progression and clarify which patients are likely to benefit from active surveillance.

"Over the past decade, the proportion of patients with low-risk prostate cancer whose disease is managed by active surveillance rather than surgery, radiation, or other treatments has gone from 10% to 40%," said Jeri Kim, M.D., a professor in the Department of Genitourinary Medical Oncology. "But there are no established selection criteria for active surveillance."

> **"Men with low-risk prostate cancer should consider active surveillance as a management option."**
>
> **– Dr. Jeri Kim**

Dr. Kim and John Davis, M.D., an associate professor in the Department of Urology, are the co-principal investigators of an ongoing trial designed to help define these criteria. The trial recently completed its enrollment of more than 1,100 patients, and the investigators have begun analyzing preliminary data.

Trial design

In 2006, the trial began enrolling patients with recently diagnosed, early-stage (i.e., clinically localized) prostate cancer who expressed a preference for

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active surveillance. All patients underwent baseline PSA (prostate-specific antigen) tests and, since 2007, transrectal ultrasound-guided biopsies of 11 cores.

Favorable-risk disease was defined as a PSA level below 4 ng/mL and a biopsy core with either (a) a tumor length less than 3 mm and a Gleason score less than or equal to 6 or (b) a tumor length less than 2 mm, a Gleason score of 7, and no dominant Gleason grade 4 (i.e., poorly differentiated) component. Patients with favorable-risk disease were classified as group 1. Patients who did not meet the criteria for favorable-risk disease were placed in group 2 if they were candidates for surgery or radiation therapy but chose active surveillance or in group 3 if they had comorbidities that precluded surgery or radiation therapy.

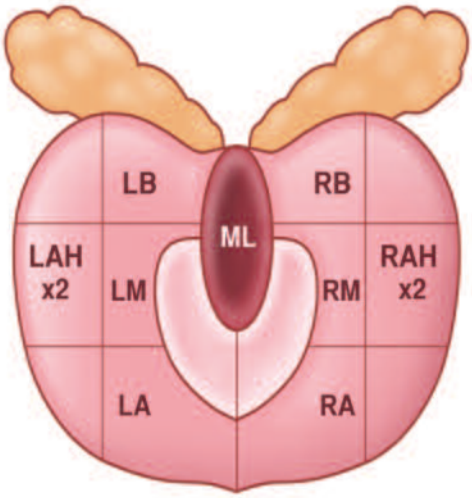
The trial's endpoints include 5- and 10-year progression-free survival rates as well as quality of life as measured by questionnaires. Concurrent studies of biomarkers for disease progression also are under way.

Surveillance protocol

"There's no standard monitoring schedule for active surveillance," Dr. Kim said. "Different active surveillance studies worldwide may use different schedules and even different surveillance tests." The tests and monitoring schedule for the trial were based on the active surveillance schedule that is typically used at MD Anderson.

In the trial, patients undergo a digital rectal examination and a blood draw for PSA testing every 6 months; at this time patients also answer a quality-of-life questionnaire. Transrectal ultrasound-guided biopsies of 11 cores are performed at the end of the first year and then every 1–2 years, depending on disease characteristics.

Patients in the trial will continue this surveillance schedule until disease progression, or "reclassification," occurs. Indications for disease reclassification are a 30% increase in PSA level or biopsy findings that indicate progression, such as an increase in Gleason score, increase in tumor length or volume in a positive biopsy core, or additional positive cores. If a patient's disease is reclassified, the patient will be offered surgery or radiation therapy.



In 11-core ultrasound-guided prostate biopsies, one or two cores are taken from each of the sites shown. Abbreviations: LB, left base; LM, left middle; LA, left apex; LAH, left anterior horn; RB, right base; RM, right middle; RA, right apex; RAH, right anterior horn; ML, midline; ×2, two cores.

Preliminary findings

Predictors of disease reclassification

To evaluate variables associated with disease reclassification in patients with the favorable-risk profile, Drs. Kim and Davis and their colleagues conducted a preliminary analysis of outcomes for 191 patients from group 1. At a median follow-up of 3 years, disease remained stable in 159 (83%) of the 191 patients and was reclassified in 32 (17%). All 32 of these patents had their disease reclassified on the basis of biopsy results. A multivariable analysis of baseline characteristics found that tumor length of 1 mm or greater in a biopsy core was a significant predictor (P = .007), older age was a marginal predictor (P = .05), and PSA level was not a predictor of disease reclassification.

More recently, the researchers analyzed the outcomes of 808 patients: 246 from group 1 and 562 from group 2. The study's results are not yet published, but Dr. Kim said that multivariable analysis showed that tumor length of 1 mm or greater in a core from the diagnostic or confirmatory biopsy performed at enrollment and assignment to group 2 were predictors of reclassification. As in the previous analysis, PSA level was not a predictor of disease reclassification. Over a 5-year surveillance period, patients with more than one positive biopsy core with a tumor length of 3 mm or more and a Gleason score of 6 or 7 at enrollment were twice as likely as patients in the favorable-risk group to have their disease reclassified.

If confirmed by analyses that include 5- and 10-year survival data, the findings from these two preliminary analyses could lead to less stringent and less invasive monitoring for patients without predictors of disease reclassification. "Our preliminary data indicate that patients with certain tumor characteristics can have less frequent biopsies," Dr. Kim said. "We're learning a lot from this study, including how to reduce the use of invasive procedures while maintaining safety."

"These findings suggest that patients tend to maintain their quality of life during active surveillance."

– Dr. Jeri Kim

A large tumor (arrows) of the anterior prostate gland is shown on multiparametric magnetic resonance imaging, which combines T2-weighted (left), diffusion-weighted (center), and dynamic contrast-enhanced (right) images and can be used with ultrasound-guided biopsy to help determine whether active surveillance or immediate treatment is appropriate. Images courtesy of Dr. Jeri Kim.

Quality of life

Another goal of the trial is to document changes in patients' quality of life during active surveillance for prostate cancer. Drs. Kim and Davis and their colleagues analyzed the scores of quality-of-life questionnaires completed over 2.5 years by 180 patients in group 1. These questionnaires assessed disease-specific and general quality of life as well as anxiety and illness uncertainty.

The mean overall scores for both disease-specific and general quality of life remained stable; only the scores regarding sexual function decreased. Dr. Kim noted that this decrease was statistically but not clinically significant. Scores for anxiety and illness uncertainty improved over time. "These findings suggest that patients tend to maintain their quality of life during active surveillance," Dr. Kim said. "But we need data for longer follow-up times."

Drs. Kim and Davis are planning another study that will compare quality of life in patients undergoing different prostate cancer treatments with that of patients undergoing active surveillance.

Biomarker study

A biomarker analysis of blood samples from 542 patients from groups 1 and 2 showed that high baseline levels of caveolin-1, a component of the caveolae and cellular membrane that is secreted by prostate cancer cells, were associated with disease reclassification during active surveillance. If validated, this finding—which Drs. Kim and Davis and their colleagues reported at the 2016 meeting of the American Society of Clinical Oncology—could lead to the use of caveolin-1 levels, in conjunction with baseline clinical and pathological parameters, to select patients for active surveillance.

Future diagnostic and surveillance tools

Although the potential prognostic factors and biomarkers for disease reclassification revealed in the trial's preliminary analyses are a few years away from validation and clinical use, some existing techniques could be applied to improve patient selection for active surveillance. For example, Dr. Kim said that multiparametric magnetic resonance imaging (MRI), which combines functional MRI with anatomical T1-weighted and T2-weighted MRI, and MRI-ultrasound fusion biopsy have improved the detection of clinically significant prostate cancers.

She added that commercially available genetic tests can give information about the aggressiveness of a patient's disease, a patient's 10-year mortality risk, or—used in conjunction with the patient's National Comprehensive Cancer Network risk stratification—the likelihood of finding favorable pathology results at prostatectomy. These techniques could soon become standard risk assessment tools for prostate cancer.

"The newer technologies will help improve the initial risk stratification to filter out those patients who may need active treatment," Dr. Kim said. "But for the most part, men on active surveillance with current technology are doing well. Men with low-risk prostate cancer should consider active surveillance as a management option." ■

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Gut Microbiome May Affect Immunotherapy Response in Melanoma

Metastatic melanoma patients who experience responses to checkpoint inhibitors have a distinct gut bacterial genetic signature

By Bryan Tutt

Changes in an individual's gut microbiome, which comprises more than a trillion bacteria and other microbes, can occur with various diseases, including cancer. While the relationship between the gut microbiome and cancer remains largely unknown, researchers have found an association between the microbiome and response to immunotherapy in patients with metastatic melanoma.

In the past few years, researchers have learned much about the gut microbiome and its role in maintaining health. So far, investigators in the United States, China, and Europe have sequenced the collective microbial genomes of hundreds of individuals and catalogued several million genes.

More recently, preclinical research has indicated a link between the microbiome and the response to immune checkpoint inhibitors in mice with melanoma. To see whether this finding could be replicated in humans, researchers led by Jennifer Wargo, M.D., M.M.Sc., an associate professor in the Departments of Surgical Oncology and Genomic Medicine and co-leader of the Melanoma Moon Shot Program at The University of Texas MD Anderson Cancer Center, investigated the relationship between gut bacterial genetic signatures and the response to immune checkpoint inhibitors in a series of patients with metastatic melanoma.

"Our findings have important implications and suggest that perhaps we should be profiling the gut microbiome of patients before treatment with immune checkpoint inhibitors," Dr. Wargo said. "Furthermore, our data suggest that we may be able to modulate the gut microbiome to enhance responses to immune checkpoint inhibitors."

Searching for biomarkers

Dr. Wargo and her team have worked to identify biomarkers of response to drugs that inhibit the immune checkpoint protein PD-1 (programmed cell death protein 1). "Anti–PD-1 therapy is effective for many, but not all, patients with metastatic melanoma," Dr. Wargo said. "And in some patients, the responses aren't durable. We want to find ways to enhance response rates as well as the durability of responses."

As part of a larger study, the researchers obtained oral and fecal samples from metastatic melanoma patients before treatment with PD-1 inhibitors. 16S rRNA gene sequencing, a standard technique for identifying bacterial taxa, was used to characterize each patient's gut microbiota.

Using Response Evaluation Criteria in Solid Tumors, Dr. Wargo and her colleagues evaluated the patients' reponses to PD-1 inhibition and divided the patients into two groups—responders and nonresponders—for analysis. "Our hope going into the study was to identify particular gut bacterial signatures that correlate with response to therapy," said Vancheswaran Gopalakrishnan, B.D.S., M.P.H., a graduate research assistant in Dr. Wargo's laboratory and a Ph.D. candidate.

Results of an early analysis of 30 responders and 13 nonresponders to PD-1 inhibition were presented at the 2017 American Society of Clinical Oncology–Society for Immunotherapy of Cancer Clinical Immuno-Oncology Symposium. While no differences were seen in the oral microbiome, responders to PD-1 inhibition had a higher overall bacterial diversity and a larger proportion of bacteria belonging to the Ruminococcaceae family in the gut microbiome at baseline compared

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"[O]ur data suggest that we may be able to modulate the gut microbiome to enhance responses to immune checkpoint inhibitors."

– Dr. Jennifer Wargo

Cancer-Related Fatigue

Tips for fighting fatigue

Fatigue is the most common symptom reported by cancer patients. Multiple factors such as pain, treatment side effects, and stress contribute to fatigue; and its management requires multiple techniques.

"Even after treatment is finished, up to 30% of cancer survivors experience fatigue," said Carmen Escalante, M.D., a professor in and chair of the Department of General Internal Medicine at The University of Texas MD Anderson Cancer Center. "But fatigue isn't something that cancer patients and survivors have to simply accept."

At MD Anderson's Cancer Fatigue Clinic, Dr. Escalante helps cancer patients and survivors develop strategies to overcome fatigue. Some of these strategies are summarized below and work for both patients and survivors, but the ideal approach to fatigue management for each person will depend on his or her symptoms.

Exercise

At first it seems odd to tell someone who feels tired to go out and exercise, but research has shown that moderate exercise helps improve a person's energy level. "Of all the techniques that have been studied, exercise has the best data to show that it can improve fatigue," Dr. Escalante said. "But it takes a couple of months of regular exercise before patients see an improvement."

The key for cancer patients with fatigue, especially those who have not exercised regularly in the past, is to start slowly by walking short distances or doing some other low-intensity activity and gradually increase the amount of exercise. Patients should consult a doctor before starting a new exercise routine.

Sleep

Lack of sleep can contribute to fatigue. Minor changes such as avoiding caffeine, nicotine, and chocolate in the afternoon and evening and turning off the television an hour before bedtime help some patients sleep better. If such changes do not improve sleep, the patient may want to be evaluated for a sleep disorder.

Save energy

Patients with fatigue can plan their activities to save energy. This planning can include setting priorities to make sure that the most important items get done and delegating some tasks to others. Activities that require a lot of energy can be scheduled for the time of day when the patient has the most energy, and rest breaks can be scheduled between tasks.

Manage stress and anxiety

Several options are available to relieve stress and anxiety, which contribute to fatigue. Relaxation techniques such as meditation or deep breathing can help reduce stress. Also, most cancer hospitals have counselors who can help patients cope with stress and anxiety. Some patients with cancer-related anxiety are given anti-anxiety medicines; however, these drugs are not appropriate for all patients.

Medicine

Medicines such as stimulants and antidepressants have been tested for treating cancer-related fatigue. However, these studies have had mixed results, Dr. Escalante said. Therefore, medication is typically reserved for patients with specific disorders that contribute to fatigue and that can be treated with the drugs.

Dr. Escalante said that antidepressants alone will not help fatigue unless the patient has clinical depression. Stimulants, however, may be used with other interventions such as exercise for patients with moderate to severe fatigue. Dr. Escalante added that insurance companies are unlikely to pay for a drug such as a stimulant unless the patient has been diagnosed with a condition the drug is approved to treat, such as attention-deficit/hyperactivity disorder or obstructive sleep apnea.

Get professional help

At any point during or after cancer treatment, patients with fatigue can ask their doctor to refer them to a clinic that specializes in fatigue management. In MD Anderson's Fatigue Clinic, about half of the patients are still receiving cancer treatment and half have completed treatment.

On their first visit to the clinic, patients are given a complete physical examination. "We do lab tests, if they haven't recently been done, to look for medically reversible problems that contribute to fatigue, such as anemia, hypothyroidism, or kidney and liver dysfunction," Dr. Escalante said.

Patients also fill out a detailed survey about their fatigue symptoms, anxiety, stress, pain, and sleep. "The survey helps us untangle this web of symptoms and develop a focused treatment plan for each patient," Dr. Escalante said. These plans usually include exercise and some of the other techniques described above. Depending on a patient's needs, he or she may also be referred to other experts, such as psychiatrists or sleep medicine specialists.

Follow-up visits are scheduled at least 6 weeks later. During these visits, the survey is repeated to monitor changes in fatigue levels. Dr. Escalante said her patients' fatigue levels typically improve over time.

"Fatigue won't always go away completely," Dr. Escalante said, "but decreasing it from a severe level to a moderate or mild level can improve quality of life." ■

FOR MORE INFORMATION

- *Ask your doctor*
- *Visit MD Anderson's Fatigue Clinic at http://bit.ly/2qbZqoG*
- *Contact the Fatigue Clinic at 713-563-7100*

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Gut Biome May Affect Immunotherapy Response

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"[D]istinct signatures exist in the gut microbiomes of responders versus nonresponders to immune checkpoint inhibitors. And these signatures may dictate response to the treatment."

– Vancheswaran Gopalakrishnan

with nonresponders. In contrast, the gut microbiome of nonresponders was enriched in bacteria belonging to the Bacteroidales order.

"Based on these findings, we feel that distinct signatures exist in the gut microbiomes of responders versus nonresponders to immune checkpoint inhibitors," Mr. Gopalakrishnan said. "And these signatures may dictate response to the treatment."

Moving forward

"Our findings indicate two areas for additional research: further characterizing the diversity and composition of the gut microbiome to predict response to immunotherapy and modulating the gut microbiome to enhance treatment," Dr. Wargo said.

Dr. Wargo, Mr. Gopalakrishnan, and their colleagues are already using multiple technologies to elucidate the mechanisms that might be involved in treatment response. For example, whole genome shotgun sequencing may reveal additional differences—including differences in functional capacity—between the gut microbiomes of responders and nonresponders in the current study.

Even as they strive to learn more about the gut microbiome's effect on treatment response, the researchers are planning a clinical trial in which the gut microbiomes of patients with metastatic melanoma will be altered to create a more favorable gut microbiome. The researchers hypothesize that this favorable bacterial genetic signature will maximize the patients' chances of a response to PD-1 inhibition. ■

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