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particular microbes or enzymes could explain why some treatments are ineffective people.

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for conditions such as cancer don't always work in the same way for everyone. Credit: John Moore/Getty

In the quest for personalized therapies, most research has focused on how an individual's genome controls their body's responses to drugs. However, there is increasing evidence that a person's unique microbiome — the population of bacteria and other microbes that live in their body — can be key to determining whether or not a drug works for their condition.

Researchers now have evidence that healthy people metabolize some drugs in different ways depending on their microbial make-up. They presented their data on 4 June at the meeting of the American Society for Microbiology in New Orleans, Louisiana.

Bacteria living in the human body will eat any nutrient that comes their way, whether it's food from the host's diet or a drug that the person is taking. But this dietary flexibility can become problematic if the microbes metabolize a drug into useless or toxic compounds.

Computational biologist Leah Guthrie at the Albert Einstein College of Medicine in New York City discussed data on a chemotherapy drug called irinotecan, which causes severe diarrhoea in some patients. Previous research in mice found that bacterial enzymes called β-glucuronidases can modify the chemical structure of irinotecan and other drugs (B. D. Wallace *et al.* *Science* **330,** 831–835; 2010). Normally, the liver detoxifies these treatments by adding a chemical group called glucuronidate. But the bacterial enzyme removes the group, turning the drug into a toxic compound.

Going with the gut

To see whether a person's microbiome affected how they metabolized drugs, Guthrie and her colleagues collected faecal samples from 20 healthy people. They treated the samples with irinotecan, and measured the compounds produced by bacteria in the samples as they interacted with the drug. The team found that 4 of the samples contained high levels of the toxic form of irinotecan, but found no significant differences between the bacterial species present in any of the samples.

When the researchers analysed the proteins produced in the faecal samples, they found that those from people with high bacterial metabolisms contained strains that made more β-glucuronidases. These people also had increased levels of proteins that transport sugar into cells, which suggests they would be more likely to absorb the toxic compound and develop gastrointestinal problems.

The researchers are now planning to collect samples from people with cancer who are taking irinotecan, to see whether this is the case, says study leader Libusha Kelly, a microbiologist at the Albert Einstein College of Medicine.

It's a nice step towards understanding how gut-bacterial enzymes interact with drugs, says Matthew Redinbo, a structural biologist at the University of North Carolina at Chapel Hill who also studies irinotecan. "Our biggest insight is to look at gut enzymes and think about them the same way as human" enzymes, he says.

Redinbo says that the liver processes many of the drugs given to patients using the chemical group removed by bacterial β-glucuronidases: this suggests that the microbiome's effects could be very far-reaching. His work in mice has found that some β-glucuronidases make similar modifications to anti-inflammatory drugs that include ibuprofen, which can cause gut toxicity when administered over long periods of time (A. LoGuidice *et al. J. Pharmacol. Exp. Ther.* **341,** 447–454; 2012).

Still a black box

Researchers have identified dozens of examples of gut bacteria that seem to modify therapeutic drugs, including some that treat Parkinson's disease and anxiety, says Emily Balskus, a biochemist at Harvard University in Cambridge, Massachusetts. She says that bacterial interference could also help to explain why animal models don't always predict drug toxicity in humans, because animals contain different microbes.

But many questions remain. Few of the enzymes responsible for breaking down these drugs have been identified, and it's unclear how much gut bacteria vary among the human population.

A paper published on 2 June in *Science*, for instance, found that the HIV-prevention drug tenofovir, which is applied to the vagina as a gel, was ineffective in women whose vaginas contained a type of bacterium

called *Gardnerella* (N. R. Klatt *et al. Science* **356,** 938–945; 2017). The bacteria quickly broke the drug down into an inactive compound, but the scientists don't yet know how the process works, or whether it can be halted.

Eventually, Balskus says, clinicians may be able to screen people's microbiomes to determine whether a drug will work for them. If their gut microbiomes seem problematic, doctors could prescribe an enzyme inhibitor or put them on a diet that provides the bacteria with an alternate food source. Studies using a dietary intervention in mice have shown some success in preventing gut bacteria from degrading a heart drug called digoxin (H. J. Haiser *et al. Science* **341,** 295–298; 2013).

Redinbo wants to try the technique in people. His start-up biotechnology company, Symberix in Durham, North Carolina, plans to apply for permission to start a clinical trial in which researchers will give cancer patients a β-glucuronidase inhibitor alongside irinotecan.

Still, it will be a long time before enough is known about bacteria–drug interactions for physicians to be able to prescribe such therapies routinely. "It's staggeringly complex," says Redinbo.