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**It’s in your blood: What your blood can tell you about your gut microbiome health**

**Shorter title suggestion:**

**What our blood can tell us about the bugs in our gut**

***Abstract (400 characters,spaces included):****The microbes in our gut are important to our health, but we do not yet know how to tell if a particular mix of microbes is "healthy". We have found that gut microbiome diversity is strongly reflected in its host by a small subset of blood metabolites, which may lead to clinical tests to monitor the health of our gut's tenants.*

**Text:**

We share an intimate symbiotic relationship with the microbes in our gut. Our microbiome helps us digest and absorb nutrients from our food, and also helps with the development and proper functioning of our immune system. Despite considerable progress in understanding the human gut microbiome, defining what constitutes a reference (‘healthy’) microbiome has proven challenging. Abundance and presence of specific microbes can vary across different geographic locations and environments, often making translation of findings from one group of individuals to another problematic. Higher level summary measures of the gut ecosystem have shown more consistent results. In particular, high gut bacterial diversity is considered beneficial, while its depletion has been associated with a number of disease conditions across populations, including recurrent *Clostridium difficile* infections, diabetes, and gastrointestinal disorders such as Crohn’s disease.

Human blood contains thousands of metabolites that we are now able to accurately measure at an increasingly low cost. Some metabolites come from our diet unmodified, others result from digestion, and another set, the "microbial" metabolites, are synthesized by the gut microbiome from the part of our food they eat. Microbial metabolites are absorbed in the large intestine and end up in the blood. It is these microbial metabolites in particular that led us to hypothesize that gut microbial structure could be measured via its reflection in the blood. Furthermore, we believed that while gut microbes in individuals may vary across environment and geography, they might have similar effects on us.

To test our hypothesis, we used a machine learning approach, which basically means that we allowed the computer to identify patterns in a ‘training’ data set, where it tried to predict gut microbiome diversity for each individual from their blood metabolite concentrations. We then applied the resulting machine learning model to a ‘test’ data set, which it had never ‘seen’ before, and we validated how accurately it was able to predict gut microbiome diversity from the same blood metabolites. To our surprise, not only were we able to predict gut microbiome diversity from the metabolites in the blood, but the prediction relied on a narrow subset of 40 metabolites (out of >650 we had measured). Nearly ⅓ of the metabolites we identified were previously shown to be synthesized by bacteria in the gut. Some of these microbial metabolites were known to be associated with negative health outcomes, such as kidney dysfunction and cardiovascular disease. Another interesting finding was that blood metabolites could predict an increase or decrease in gut microbiome diversity under varying conditions, like antibiotics treatment or gastrointestinal disease, and this prediction was robust in an independent cohort of different individuals. Lastly, one of the surprising findings was that the blood metabolites did better at predicting gut microbiome diversity than an extensive panel of blood proteins and even clinical labs. The lack of gut microbiome reflection in clinical labs was particularly striking, as they are the present standard used by doctors for monitoring health.

Our approach allowed us to examine which metabolite concentrations in the blood change in people with lower or higher diversity. We found support for the known association of lower gut microbiome diversity with antibiotic use or with negative health measures such as diarrhea. We also identified several metabolites which may exert potentially toxic effects in the host as associated with higher diversity, including p-cresol sulfate and trimethylamine N-oxide (TMAO). Therefore, there may exist a ‘Goldilocks Zone’ for gut microbial diversity, whereas neither high nor low diversity represent optimal health.

An important implication of our work is the early diagnosis of the recurrent form of *Clostridium difficile* infection, which accounts for ~15,000 deaths annually in the U.S. One of the primary risk factors for recurrent *Clostridium difficile* infection is low gut microbial diversity, often brought on by antibiotics or other medication use. A reliable clinical blood test for gut microbial diversity would allow us to screen individuals at higher risk for recurrent (i.e antibiotic-resistant) infections and perhaps employ more effective therapies, such as fecal transplants, as a first line of treatment.

Future work is needed in order to untangle the health effects of the complex relationship between the gut microbiome and human health. We believe that the key to defining and monitoring a healthy state of the microbiome is examining its reflection in the blood, which may be more stable, quantifiable, and universal.

***Suggested Image:***

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***Image credits:*** *Allison Kudla*