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# Diagnosing cancer by microbial signatures

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*Cancer tissues are often thought to be sterile entities in the human body, exempt from the influence of our microbial cohabitants. To test this theory, we examined genetic information from patients' tumors and blood and discovered cancer-specific microbial communities among more than 30 cancer types. This study proposes a new class of microbial-based cancer diagnostics.*

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When was the last time your oncologist talked to a microbiologist? For most, this question seems unusual, as if cancer care had little to do with the communities of microorganisms (microbes) that live together with us, called microbiota. Indeed, the last three decades of cancer research have focused on characterizing the human side of cancer — how the human genes mutate and lead to tumor formation, how the immune system fails to prevent abnormal cell growth, and so forth.

Yet, microbes have dominated the history of life on earth and consistently found ways to adapt to even extreme environments, such as dangerously low/high temperatures and very high pressures. There are also roughly the same number of microbes that live on and inside our bodies as we have human cells. We thus hypothesized that microbes may exist and even survive within cancerous tumors. If so, characterizing their presence and function could be useful to develop new cancer diagnostics and treatments.

To test this hypothesis, we re-examined one of the largest cancer studies ever conducted, The Cancer Genome Atlas (TCGA) project, which comprises a catalog of comprehensive genomic datasets from over 10,000 patients and 33 cancer types. Scientists often use the TCGA dataset matching the human genome, the entire set of human genetic information, ignoring the rest ("non-human" information). In contrast, we discarded human-

associated genetic data in this cancer database and looked at the remaining "non-human" data that may include microbial information.

These analyses required running a supercomputer for six months straight to extract all the microbial genetic information from around 18,000 cancer-associated samples in TCGA. After all of this computing, we found that 2.5% on average of the cancer genomic information was actually microbial in origin. The data also showed that cancer type accounted for a large amount of variability, suggesting that cancer-specific microbial populations may exist. Testing this hypothesis with further analyses revealed that microbial populations alone were capable of diagnosing different cancer types. Collectively, these results proposed that each cancer type had a unique microbial community and that this information could potentially be used as a new diagnostic.

Taking microbial genetic information from a cancer to diagnose the cancer was somewhat self-defeating, however, as oncologists would already know the cancer type by that point. A more useful cancer diagnostic would detect it without directly sampling the tumor, such as with a blood test. Since cancer genomic information is known to leak into the blood of patients, we similarly wanted to check whether microbial genetic information is also present there. Moreover, clinical evidence from the last 50 years has shown associations between certain microbes found in the patients' blood and later colon cancer diagnoses in those same patients, supporting this idea. Since the TCGA dataset also included about 1900 blood samples from cancer patients, we applied our same analytical methods as before to see if microbial genetic information in blood could also diagnose cancer type. Since contamination can influence these results and mislead conclusions, we further developed a way to identify and remove contaminating (cancer-unrelated) microbial genetic information. Surprisingly, we found that it was still possible to tell which cancer type a patient had (out of 20 cancer types) solely on the basis of microbial genetic information in blood. These findings highlighted a potentially new way to diagnose cancers with minimal invasiveness, using just a few milliliters of blood.

To show that these findings were generalizable, we looked for microbial genetic information in plasma samples (a component of blood) from 100 cancer patients from prostate, lung, and skin cancers, and 69 non-cancer individuals. We additionally included dozens of contamination controls to make sure that the data were reliable. Analogous to the TCGA findings, we could distinguish which cancer type a patient had solely using microbial genetic information from their plasma. It also showed that patients with cancer could be distinguished from patients without cancer in a similar manner. Collectively, these analyses suggested a fascinating opportunity to build human cancer diagnostics out of non-human, microbial genetic information.

Overall, this study provides the most comprehensive analysis of cancer-associated microbes to date and forms an atlas for future cancer researchers. We have made the findings interactively accessible online, and we hope that future cancer studies will consider how to utilize microbial information in their analyses too. Perhaps not too far in the future, your oncologist will indeed have a good reason to see a microbiologist.