Going big by going small: trade-offs in microbiome explanations of cancer

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PREPRINT—forthcoming in *Studies in History and Philosophy of Science* (accepted Dec. 2022)

Abstract

Microbial factors have been implicated in cancer risk, disease progression, treatment and prevention. The key word, however, is "implicated." Our aim in this paper is to map out some of the tensions between competing methods, goals, and standards of evidence in cancer research with respect to the causal role of microbial factors. We discuss an array of pragmatic and epistemic trade-offs in this research area: prioritizing coarse-grained versus fine-grained explanations of the roles of microbiota in cancer; explaining general versus specific cancer targets; studying model organisms versus human patients; and understanding and explaining cancer versus developing diagnostic tools and treatments. In light of these trade-offs and the distinctive complexity and heterogeneity on both sides of the microbiome-cancer relationship, we suggest that it would be more productive and intellectually honest to frame much of this work, at least currently, in terms of generating causal hypotheses to investigate further. Claims of established causal connections between the microbiome and cancer are in many cases overstated. We also discuss the value of "black boxing" microbial causal variables in this research context and draw some general cautionary lessons for ongoing discussions of microbiomes and cancer.

Keywords: microbiome, cancer, causal explanation, trade-offs

Introduction

Several specific microbial taxa play known causal roles in initiating specific types of cancer.[1] In addition, there is a growing body of work seeking to understand the extent to which our microbiomes—the microbial communities living in and on host organisms such as ourselves—might play a role in cancer promotion, prevention, progression and chance of recurrence (McQuade et al. 2019; Xavier et. al. 2020; Cullin et al. 2021; Sepich-Poore et al. 2021). This research focuses especially on the potential to develop personalized treatments to mitigate

[1] Of eight classified "oncomicrobes" one species, *H. pylori*, is bacterial, and the rest are viral (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012). The historical context of their discovery is fascinating and often fraught with controversies; some of these parallel, and others differ from, current work on the cancer-microbiome connection which is our focus here. For further insight on historical cases of cancer virus discovery see Becsei-Kilborn (2010), Sankaran (2021) and Morgan (2022).

harmful impacts, or promote beneficial impacts, of particular microbiome states or compositional signatures.[2]

It is poorly understood whether and how microbiomes and cancer are causally related, as researchers in this area acknowledge:

> "Although the link between the microbiota and cancer has been recognized... The functional relevance of human microbiomes to cancer development has not been established" (Schwabe and Jobin 2013, p. 808).

> "Disentangling causality from correlation, given the diversity in sequencing and data collection methods, represents a formidable challenge to the field [of cancer microbiome research]" (Cullin et al. 2021, p. 1319).

> "The proof of cancer causality for each of these microbes [characterized in relation to colorectal cancers], in main, remains indirect" (Alhinai et al. 2019, p. 5).

> "[U]nderstanding of [a] direct role for pathogenic bacterial infection is [a] point of doubt due to vast effects of bacterial infection on manipulation and exploiting of human host cell niche in numerous approaches throughout different stages of infection cycles" (Eyvazi et. al. 2020, p. 1).

At the same time, bold claims abound suggesting causal roles for microbiomes in cancer causation, and in potential avenues of prevention or treatment. Sometimes both sorts of claims appear in the same paper. Cautious claims such the last two quoted above are found in papers with titles like "The role of the gut microbiota in colorectal cancer causation" (Alhinai et al. 2019) and "The oncogenic roles of bacterial infections in development of cancer" (Eyvazi et. al. 2020); the former is framed as a review of "emerging evidence on the role of the microbial community in colorectal carcinogenesis" (Alhinai et al. 2019, p. 1).

Neither the cautious claims nor the casually suggestive claims should be cherry-picked or taken out of context. We mention both at the outset to illustrate the tension in this literature between highlighting the prospects of microbiome-cancer connections while also exercising appropriate care not to overstate the implications of findings to date.

Our goal in this paper is to examine particular issues that arise at the intersection of microbiome and cancer research. We see our work here as building on prior work by philosophers on trade-offs, as well as contributing to recent philosophical discussions of both microbiome research and cancer research (e.g., Rondeau et al. 2019; Sholl 2022; Laplane et al. 2018, 2019), in the spirit of Longino's practice-centered philosophy of science (Longino 2016). Longino defends this approach because it allows for critical reflection on how evidence is brought to bear on various claims, as well as what assumptions or presuppositions are "involved in treating the data as evidence." We discuss three trade-offs at play in investigating causal relationships between microbiomes and cancer, examine how the context of this research provides grounds for

[2] A note on our microbiological terminology: we use the terms 'microbiome' and 'microbiota' to refer collectively to all of the microbes living in and on a human or other host organism (or in a specified location in a host's body, for example, the gut microbiome or tumor microbiome). We use 'microbes' or 'microbial taxa' to refer to a subset of the microbiome, including specifically identified taxa (such as *E. coli*).

exceptional concern about causal attribution, and recommend some strategies for framing and interpreting findings in light of this discussion.

The first trade-off concerns the causal and outcome variables. Some researchers seek to demonstrate a role for "the microbiome" as a whole, whereas others look to more fine-grained causal variables, such as the role of particular microbial taxa in cancer initiation or responses to treatment. Looking for patterns of association between whole microbiome features and various outcomes can be useful in generating more fine grained hypotheses or describing potentially fruitful interventions. However, we urge caution in evaluating explanatory and predictive generalizations from such associations. Relatedly, there are trade-offs between research concerning open-ended or coarse-grained outcomes, such as cancer risk as a whole, and finer-grained outcomes, such as risks of particular cancers, or responses to specific treatments in specific cancers (for example, immune therapies in melanoma).

A second trade-off regards the relationship between the object of study and the target populations of interest. Sometimes these relationships are close; other times they are more distant. However this trade-off goes, it is important to avoid overstating the extent of the analogy or overlap in relevant mechanisms and pathways in model organisms or human research subjects and target populations. This issue relates to, and in at least some cases amounts to, the problem of external validity.[3] However, sometimes the challenges have to do with the particular context sensitivity of causal relationships in the cancer-microbiome matrix: for example, thresholds for activation of various causal pathways in cancer are controlled in very context-specific manners, and so extrapolation from one context to another is especially fraught (see, e.g., Bechtel 2018, 2020).

Last but not least, there are trade-offs between the goals researchers may be interested in pursuing: developing clinical applications versus identifying putative causal pathways between the microbiome and cancer. More thorough mechanistic understanding, and appreciation of the heterogeneity of pathways even within the same cancers, can help correct for over-generalization and ensure that ensuing recommendations don't overstate risk or benefit.

Of course, it would be ideal if research on the microbiome and cancer addressed both fine-grained and coarse-grained dependent and independent variables, conducted studies of both models and human patients, and sought better explanations, diagnoses and treatments. While these are not necessarily trade-offs for the field as a whole, they are for individual researchers or groups: a single line of inquiry typically cannot address both sides of a trade-off simultaneously.[4]

As Matthewson (2011) points out in a discussion of trade-offs in model building, trade-offs might be superficial, due only to our current practical or cognitive limitations, or they might be "deep," unavoidable even in an ideal scenario of unlimited resources (cognitive, technological or otherwise). While the trade-offs we discuss differ from trade-offs in model building in important

[3] See Cartwright (2010) for pertinent discussion; see also Parke (2014) for discussion of how external validity or inferential power does not necessarily track the intuitive "closeness" of an object of study to the target of inquiry.
[4] And of course, a competitive funding environment means that choice of research question, target outcome, or experimental or model system is always constrained financially. Practical, diagnostic, or therapeutic implications are often framed as goals, even for research with no clear clinical implications, exactly in light of this competitive environment.

respects, Matthewson's graded scale from more superficial to deep is useful here in mapping out the variety of pragmatic and epistemic challenges at stake. All three trade-offs we discuss are at least pragmatic: it can be difficult or impossible to achieve both aims simultaneously, given limited resources and a researcher's goals (for example, clinical medicine versus public health). In such cases, prioritizing one aim over another is the only option. However, sometimes apparently pragmatic trade-offs are not merely pragmatic. Many of the cases we discuss here have to do with downstream epistemic concerns about causal attribution. For example, pragmatic choices can lead to overstated conclusions or overrepresentation of some causes over others, by the researchers themselves or by science communicators, philosophers, historians and others engaging with scientists' work.

The trade-offs we discuss are common in biological and biomedical research (Levins 1966; Smith 1988; LaFollette 1996; Steel 2008; Matthewson and Weisberg 2009; Degeling and Johnson 2013; Stegenga 2018). However, to our knowledge, these trade-offs have not been discussed in the philosophical literature as they arise in the context of cancer microbiome research, where they present some distinctive challenges.

For one, this context presents a "perfect storm" for causal misattribution and overblown claims. It brings together two research areas where causal attribution, and separating correlation from causation, present major problems on their own within each field, with potentially serious consequences for human health (Sekirov et al. 2010; Hanage 2014; Hacquard et al. 2015; Fischbach 2018; Gilbert et al. 2018; Plutynski 2018; Lynch et al. 2019, 2020; Walter et. al. 2020). As both microbiome research and cancer research are of significant current interest, it is especially easy to get carried away with claims about their various findings and implications (see, e.g., Lynch et al., 2019; Parke 2021; Shanahan et al. 2021), a point which is arguably compounded at the intersection of these fields. Overblown or otherwise less than careful claims—not only by scientists but also by the press, and philosophers and historians of science—raise the potential for public misunderstanding.

Another distinctive feature of this context is the extreme heterogeneity on both sides of the microbiome-cancer equation. Any claim about "the microbiome and cancer" can immediately mislead by suggesting that either of those terms, as such, points to a specific explanatory factor or disease type. As we elaborate on below, microbiomes vary within individual hosts from one organ or micro-environment to another, within individual hosts over time, and across individuals. Microbiome research findings also focus variously on entire microbial communities living in or on a host's body, microbial communities localized in particular organs or parts of a host's body, or sometimes specific community members (microbial taxa). Cancers are also remarkably heterogeneous, involving different organs and tissues throughout the body and complex, dynamic relationships to the tumor microenvironment (Laplane et al. 2018, 2019; Plutynski 2018, 2021; Rondeau et al. 2019). In conditions of such heterogeneity, it is all the more important, and more challenging, for researchers to be clear about whether they have established mere causal relevance, causal tendency, or identified the specific causal role of a variable in a given context. The values of variables change, either across tumor type, local context, or at different stages of cancer progression (early initiation versus dissemination and metastasis). A given variable can be expected to act differently in different background conditions, and so it is

important to specify whether one is referring to mere causal tendency, or token causal relationships with specific values attached to specific variables.[5]

A call for more clarity here is warranted further in light of recent trends of overstatement and misinformation in public-facing portrayals of research on the microbiome and disease, which can have serious consequences (Eisen 2018). To cite just one example: A popular science article titled "Possible link between bacteria and breast cancer: study" announced "Groundbreaking [research] looking at the role bacteria may play in breast cancer" (Sims 2014; see also Eisen 2014). The study referenced in this article showed minor differences in the abundance and taxonomic identity of bacteria found in cancerous as opposed to non-cancerous breast tissue; it showed no specific causal role for bacteria in breast cancer. The authors of the original study were explicit that their aim was to show that there *is* a breast microbiome—not to claim any causal link between microbes and breast cancer (Urbaniak et al. 2014). Even the most carefully framed studies are at risk of misconstrual, which is all the more reason to maintain clarity and a critical eye in framing and interpreting the causal claims at stake.

The rest of this paper proceeds as follows. In Section 1, we discuss the first trade-off regarding coarse-grained versus fine-grained variables, such as the microbiome as a whole versus specific microbial taxa, or cancer as a whole versus more specific outcome variables. We also consider challenges in defining and measuring "dysbiosis," and in determining whether microbial variables, at any level of grain, are causally relevant to disease outcomes. In Sections 2 and 3, respectively, we consider trade-offs between studying human patients versus model systems, and explaining versus diagnosing or treating cancer. In each of these sections we discuss a few studies to illustrate our points; this is not to single out these studies as special targets of criticism, but rather with an eye to examples that illustrate the range of issues at stake. Finally, in Section 4, we draw some lessons about difficulties in establishing causal claims and the value of "black boxing" microbial causal variables in this research context. We conclude with cautionary notes for framing and interpreting future causal claims about microbiomes and cancer.

While we make some recommendations conditional on researchers' aims throughout, we do not want to suggest that one option is always best on any of the three trade-offs. Our goal is to diagnose these trade-offs, examine their interplay at the intersection of microbiome and cancer research, and call for more explicit acknowledgement of them in these discussions and thereby greater clarity regarding the putative causal relationships at stake. This gives rise to some particular recommendations for scientists in framing causal claims, and philosophers, historians and others in interpreting those claims.

[5] Plutynski (2018) makes these points regarding the appropriate interpretation of scientific claims concerning the causal role of genes in cancer. A cause can be relevant to some outcome without yet specifying the way in which it is relevant (its "role"); something can be a causal variable or can take a specific value or range of values; a cause can have different effects in homogeneous versus heterogeneous background conditions; and reference to a cause may be to a causal tendency or a token event or change in variable value. Rondeau et al. (2019) describe how causal inquiry in cancer requires attention to many factors that vary across contexts (see also Laplane et al. 2018, 2019). Our argument builds on these insights, demonstrating how distinctive challenges arise in establishing the causal role or relevance of microbial factors in cancer, and urging more precision along the suggested lines.

1. Coarse-grained versus fine-grained variables

A first question we can ask in this research context concerns how coarse-grained versus fine-grained the explanatory and target variables are. Are we talking about an entire microbiome or something more specific? Are we talking about microbiome composition or specific functional interactions between microbial taxa and their causal role in disease? Are we talking about cancer risk at large, particular cancers, or subsets of particular cancers?

Sometimes microbial variables are fine-grained and specific in referring to a particular microbial taxon or set of taxa. Sometimes they are coarse-grained to the point of being unhelpful or misleading. A number of researchers have made bold claims about the role of "the microbiome" in cancer, and indeed in all of human disease. A vivid example of the latter is Pitlik and Koren's (2017) call for "a unifying scheme of disease," according to which "probably every illness of holobionts is characterized by some perturbation of the microbiome/microbiota into a pathobiome" (p. 1) ('holobiont' refers to the composite of a multicellular organism and the symbionts living within it, for example, a human including our microbiome). As the authors of such claims themselves acknowledge, the problem with such hypotheses is that as yet, scientists lack a good understanding of what "normal" microbiomes are like (more on this in Section 1.1). It's far from clear that the idea of a "normal" versus "unhealthy" whole microbiome can meaningfully be deployed as an explanatory causal variable.

There is a second sense in which microbial variables can be finer or coarser grained: in referring to microbiomes as wholes—all of the microbes living in and on a host organism—or to more localized microbiomes, such as the gut or vaginal or oral microbiome. This comes up specifically in cancer research in studies of local microbiomes and cancers in the same location (for example, the gut microbiome and colon cancer) and of tumor microbiomes; more on this in Section 3.

Turning to the outcome or target variable, this can also be understood at various levels of grain. Some discussions apparently regard the human microbiome, in a coarse-grained sense, and cancer (or cancer risk) as a whole, as opposed to specific cancer types or subtypes or specific features of cancer. This is the implication of article titles such as "Microbiota effects on carcinogenesis: initiation, promotion, and progression" (Lopez et. al. 2021), "The cancer microbiome" (Elinav et al. 2019) or "The human microbiome in relation to cancer risk" (Huybrechts et al. 2020). But when one reads these articles more carefully, the causal and outcome variables at stake in any given study are typically much more specific. Some studies focus on specific microbes associated with specific cancers, such as *HPV* and cervical cancer or *H. pylori* and stomach cancer. Others focus on microbial explanations of chemotherapy resistance in colon cancer (Riquelme et al. 2019) or patient responses to a particular melanoma treatment (Baruch et al. 2020). This tension between what researchers suggest the explanatory variable is in their article title, abstract, introduction or discussion, and what they are in fact measuring or intervening on, is one source of misunderstanding and overblown claims in both popular and scientific literature (see Riquelme et al. 2019; Kadosh et al. 2020).[6]

[6] We do not mean to suggest that these sorts of article titles or introductory discussions are intentionally misleading. But even if 'the microbiome' is being used as shorthand (e.g., for a microbial causal core in the sense of Lynch et al. 2019), the resulting claim misleads by apparently regarding whole microbiomes rather than particular microbes. Perhaps this involves something like "microbial synedoche", or using 'the microbiome' to stand in for the parts of

Fine-grained interventions and fine-grained outcome variables are intuitively appealing. We might think: shouldn't researchers always be aiming for fine-grained mechanistic knowledge? Wouldn't we prefer to know which specific microbial taxa are causally responsible for which specific cancer outcomes? However, depending upon researchers' interests and aims, it is at least sometimes warranted to prioritize attention to general patterns over more specific mechanisms, pathways, or targeted experimental interventions.

In recent work, Lynch and colleagues (2019) criticize current trends in microbiome research, arguing that the causal explanations on offer are often weak or misleading. Sometimes 'the microbiome' is used as shorthand for what is actually a black-boxed particular subgroup or "causal core" group of microbes. In such cases, Lynch and colleagues argue, it is important to make this black-boxing explicit (2019, 2020). More generally, they argue that "the microbiome" as a whole is a poor basis for most of the sorts of causal explanations sought in human microbiome research, and they suggest focusing instead on more fine-grained microbial variables, characterized compositionally or functionally (or both).

Attah and colleagues (2020) respond that whether it makes sense to choose a more fine-grained versus coarse-grained explanatory variable "is (in part) a pragmatic matter: it depends on what we want to intervene upon, and how, given our current best understanding and tools" (p. 2). Even when fine-grained causal variables are available (for example, when we can identify specific microbial taxa), researchers might have pragmatic reasons to prefer coarser-grained variables, such as when a clinical intervention can be achieved only at that coarser level of grain. As an analogous example: one might choose to attend to coarse-grained causal variables like "dietary patterns" rather than specific, individual nutrients because research has shown that one's diet as a whole (the variety, proportion, and portion size of different foods) is as important, if not more important, to long term cancer risk than any individual nutrient (Steck and Murphy 2020). Thus, a focus on public health interventions may lead one to prioritize coarse-grained causal factors (see DiMarco 2021), at least in some specific contexts of explanation or prediction.

We will elaborate further on this point in Section 4. Let us now take a closer look at one of the most coarse-grained and controversial examples of an alleged microbial causal variable: dysbiosis.

1.1. The microbiome and "dysbiosis": cause or effect?

"Dysbiosis" is typically understood to refer to some perturbation of the microbiota, compositionally or otherwise. The general idea is that a "disturbed" or perturbed microbiome is responsible for a particular disease, or disease at large.[7] However, the very notion of dysbiosis is ambiguous and conceptually problematic (Olesen and Alm 2016; Hooks and O'Malley 2017).

the microbiome that we can currently look for. David Kelley and Jacqueline Wallis (personal communications), respectively, suggested the latter helpful ways to think about these claims.

[7] The concept of dysbiosis links to the idea mentioned earlier of a "pathobiome" (Pitlik and Koren 2017).

First, regarding ambiguity: the term 'dysbiosis' is not used consistently in the scientific literature. Hooks and O'Malley (2017) surveyed over 9,000 PubMed abstracts in which the MeSH[8] term 'microbiota' appears and found that around 5% of them used the term 'dysbiosis'. Many of the latter did not define 'dysbiosis' explicitly, and those that did gave different definitions: "as general change in the microbiota composition (e.g., alteration, perturbation, abnormal composition, and loss of diversity),[9] as an imbalance in composition (almost always deemed to have negative effects), and as changes to specific lineages in that composition (any named taxon change)" (p. 4). These senses, while overlapping, are far from consistent, and as yet there is no precise measure or definition of imbalance. Similarly, Oleson and Alm (2016) identify clusters of overlapping use of the term 'dysbiosis', from imbalance between beneficial and harmful microorganisms, to mere differences in microbiome composition, to changes in abundance of single pathobionts.

Second, the notion of dysbiosis is conceptually problematic. It is sometimes identified as both a cause and an effect of disease, often in a way that suggests that dysbiosis itself (without any further specified causal mechanism) is causally explanatory. As Oleson and Alm put it, dysbiosis is treated as "a 'mechanism-free' cause of disease to which we can retreat when plausible mechanistic explanations are discounted" (2016, p. 1). A related conceptual difficulty is that discussions of dysbiosis presuppose that researchers are in a position to say what "the healthy microbiome" looks like, assuming such a thing exists. Yet there is massive variance among healthy individuals in microbiome composition consistent with health, across industrialized and non-industrialized societies, as well as variance within healthy individuals, over time, in microbiome composition (Wilmanski et al. 2021). This suggests that no single microbiome compositional signature, or specific collection of microbial taxa, corresponds to some generic healthy state. Indeed, variation in the distribution of microbial taxa over a lifetime, rather than stability, has been found to be associated with greater health (Wilmanski et al. 2021).

This is not to suggest that there is no such thing as more or less "healthy" microbiome compositions, at least in a contextualized sense; there may well be states that are meaningfully described as such. However, whether and when microbiota promote health is likely context-dependent (Shanahan et al. 2021). Another recent study analyzed the three largest microbiome genomic data repositories and found that over 71% of the available samples are from the USA, Canada and Europe. So, "the global distribution of human microbiome sampling is heavily skewed towards North American and European populations… since only a subset of the world's populations are currently being studied, microbiome-disease associations identified may not hold up in under-sampled populations" (Abdill et al. 2022, p. 5). We ought to be cautious about extrapolating from current databases to generalize about microbiome causal factors in different cultural or environmental settings.

Furthermore, attention to particular taxa or compositions of taxa may be less important than attention to distinct suites of functions. As Shanahan and colleagues (2021) argue, we should shift attention to functional disruption involving microbiota, rather than "dysbiosis" writ large.

[8] Medical Subject Headings; see, e.g., https://onlinelibrary.wiley.com/doi/full/10.1111/ijcp.12767.

[9] Loss of diversity is typically treated as a generic cause for concern in discussions of dysbiosis. Interestingly though, in some cases such as bacterial vaginosis, *increased* microbial diversity is the reason for health concern (see, e.g., Oakley et al. 2008). Thanks to Jacqueline Wallis for suggesting this example.

This is an especially apt point in the context of cancer. Disruption to function (whether metabolic, endocrine, or immune response) is often key in initiating cancer, or shaping cancer dynamics, progression, invasion, and ultimately responses to treatment.

Claims about "the" role of the microbiome in cancer based on thin evidence can become widely accepted as uncontroversial. Researchers in this area, and historians and philosophers of science writing about this area, thus ought to interrogate these claims very carefully. As a final example, talk of the "equilibrium" between host and microbiome as "maintained by a delicate interplay" (Komorowski and Pezo 2020) is misleading. Mere increase or decrease in the population size of a given microbial taxon need not disrupt health. While at least some of our resident microbes surely play key roles in our health or risk of disease, there is ample variation across human individuals and populations in microbiome species composition and functional diversity.

1.2. Cause, complicit actor, passive bystander, or effect?

In drawing implications from this research for cancer prevention or treatment, it is crucial to understand the extent to which there is a causal story being revealed at all, as opposed to a promising association potentially worth investigating further. For microbial variables at any level of grain, we can ask whether the microbiota in question are indeed a *cause* of the outcome variable of interest, in the sense that intervening on this variable changes the probability of the outcome occurring, a "complicit actor" promoting carcinogenesis only in combination with other factors, or merely a "passive bystander" associated with cancer (the latter two terms are from Sepich-Poore et al. 2021).

Many discussions could be clearer about which of these options they have in mind. For example, some appear to treat complicit actors and passive bystanders as equivalent: "Additional examples of carcinogenesis *promoted by* specific bacterial pathogens [include] gallbladder cancer (that is *associated with* chronic *Salmonella enterica* subsp. *Enterica* serovar Typhi and *Salmonella enterica* subsp. *Enterica* serovar Paratyphi infections…)" (Schwabe and Jobin 2013, p. 802, emphasis added). The more we move towards the passive bystander end of the spectrum, of course, the greater the risk of confusing correlation and causation.

Sometimes it is impossible to separate the putative effect from the cause. It is not always clear whether some change in microbiota state is causally responsible for cancer, or whether the cancer, or cancer treatment, causes a change in microbiota. For instance, in a paper titled "The microbiome and cancer" (Schwabe and Jobin 2013) there is a section called "Cancers promoted by dysbiotic microbiomes," suggesting microbiota are at least complicit actors in particular cancer types. The first sentence of the section reads: "A wealth of studies in patients and mice has linked the microbiota to colorectal carcinogenesis" (p. 802). Only one study is cited, which concerns colitis-associated cancer (CAC), a small subgroup of colorectal cancers (Grivennikov and Cominelli (2016) estimate CACs comprise 2–3% of overall colorectal cancers). Moreover, the cited study (Grivennikov 2013) discusses microbiota as one among many other factors that can promote inflammation, which, in turn, can promote CAC. Grivennikov writes: "[The] important question is whether microbes specifically found to be enriched in tumors always play *some* role in tumor promotion or sometimes are just *innocent bystanders*, which prefer a niche

created by [the] tumor but not normal environment... microbes play important and not entirely understood roles in IBD [inflammatory bowel diseases] and CAC" (2013, p. 11, italics added). The causal arrow regarding microbiota and (one rare form of) colorectal cancer, in this case, could just as well go in either direction—if there is a causal story to be told there at all.[10]

Many studies look at how microbiota composition affects response to treatment, measured in years (or months) of cancer-free survival or time to recurrence after treatment. There are a variety of concerns one could raise about whether the latter sorts of proxy or "surrogate" measures track outcomes that we care about in cancer treatment (see, e.g., Kovic et. al. 2018; Stegenga 2018; Prasad 2020). In any case, when patients have undergone extensive treatment, their microbiome composition might well have already been altered. Separating the effects of treatment from the effects of microbial composition, as such, is difficult. Moreover, as discussed above, individuals' microbiomes change over time, whether over the course of a day (Thaiss et. al. 2015) or a lifetime (Wilmanski et. al. 2021). A single snapshot of microbial composition, for example in pancreatic cancer patients versus controls, is unlikely to be very informative about potential effects on cancer risk, prevention and treatment options.

Other studies look at associations between, for instance, the onset and development of cancer, and risk factors such as obesity, diabetes, metabolic syndrome, or chronic pancreatitis, all of which have been claimed to be associated with gut dysbiosis (Petersen and Round 2014; Alhinai et al. 2019). Whether such associations support the claim that gut dysbiosis facilitates cancer development is far from clear, especially where evidence connecting these is exclusively correlational.

In the context of breast cancer, a positive correlation with obesity has long been observed. There are also data connecting the gut microbiome to obesity. But this does not demonstrate that "dysbiosis" in the microbiome causes breast cancer. That breast cancer patients typically have diminished gut microbiome diversity and increased levels of certain microbial taxa compared with controls, moreover, could be explained by changes in patients' diet during treatment, or the fact that breast cancer treatment often involves combinations of powerful drugs, such as doxorubicin and cyclophosphamide; these could affect microbial diversity indirectly by affecting diet, or directly, in virtue of the effects on the life cycle of cells and tissues in the gut. It is also possible that obesity, breast cancer, and particular microbiome signatures are all consequences of some other independent causal factors, such as hormonal, genetic, or environmental factors. In other words, there are a whole range of possible causal stories connecting the variables of microbiome diversity, obesity, breast cancer, and breast cancer treatment, which cannot be ruled out by correlational studies of association between microbiome diversity and cancer.

One promising way to distinguish effects from causes is to do longer term prospective cohort studies that track changes in the microbiome and cancer over time, as well as cancer incidence, progression, and potentially treatment effects. One example of such research underway is the Southern Community Cohort Study (https://www.southerncommunitystudy.org/). Gut microbiome sequencing over the course of research has the potential to track longer term effects on cancer risk. While this study is still in progress, it is a good example of the prospective cohort

[10] There is also the third option of an unknown common cause, meaning the microbes in question are themselves neither a cause nor an effect of cancer. Thanks to an anonymous reviewer for emphasizing this option.

design that could result in some more persuasive evidence of causative links between the microbiome and cancer.[11]

While many of our examples above demonstrate overstatement of causal significance, it is worth mentioning cases where researchers approach these cause and effect relationships between the microbiome and cancer with admirable caution. The paper mentioned in the introduction by Urbaniak and colleagues (2014) is one such example. The paper itself is cautious about the causal relationships involved; for example: "While a comparison between tissue from cancer patients and healthy women was not the focus of this study, we did notice a higher abundance of *Escherichia coli* in women with cancer than in healthy controls, with this species known for its cancer-promoting activity… However, it is premature to suggest a cause-and-effect relationship before more work is done in this area" (p. 3013). Unfortunately, even very careful work such as this is liable to be misconstrued as establishing a link between microbiota and cancer. A more cautious approach to take with these sorts of findings would be to frame them in terms of promising causal hypotheses to investigate as a next step.

2. Humans versus model systems

Let us turn to the experimental methods aimed at investigating these questions, and in particular, trade-offs in choice of study system. We discuss the trade-off between studying model systems versus human patients through the lens of several case studies. We then elaborate on one of these case studies to tie together some threads from the discussion, so far, of trade-offs 1 and 2.

Like our other trade-offs, this one is at least pragmatic in several respects: a given researcher, study or laboratory typically has to pick one option (studying model systems or human patients) and not the other. Both options involve some epistemic sacrifice. As the cases below illustrate, researchers might learn a lot from animal models, often benefitting from the greater opportunities for interventions compared to studies of human volunteers. But we cannot be sure the results carry over to human patients. Studies of human patients, on the other hand, are often based on associations rather than interventions, and often take place in relatively small samples. While researchers can be sure that the studied patients have the same type of cancer as their target populations, it is not a given that their microbiomes are representative of human populations at large (see Section 1.1). Both options limit researchers' ability to attribute clear general causal patterns regarding microbiomes and cancer.

Despite the frequency of mouse and other animal models of cancer and other human diseases, it is wise to be cautious in general when extrapolating from rodents to humans (Piotrowska 2013; Ankeny and Leonelli 2020; Dietrich et. al. 2020). All else being equal—ethics and feasibility issues aside—human patients would be the ideal subjects for learning about human cancer. Of course, all is not always equal.

With an eye to mitigating issues with external validity, researchers often study Human Microbiota-Associated (HMA) rodents, first transferring human fecal microbiota to germ-free mice and then checking to see if diseases or other states of interest transfer along with them

[11] We thank Liz Mallott for this example.

(Park and Im 2020; Walter et al. 2020). Walter and colleagues (2020) systematically review 38 HMA rodent studies on the role of the microbiome in human disease and find that 36 of these studies found positive results; that is, the pathological phenotype successfully transferred from the humans to the rodents. Apart from these numbers raising concerns about the "file drawer" effect (the lack of publication of negative results) and about confusing correlation with causation, there are several reasons the authors caution against extrapolating to causal claims about the role of the relevant microbiota in human disease. First, human microbiota vary across individuals and over time in the same individual. Second, causal relationships between microbiota and disease are rarely simple; they often involve synergistic effects of interactions between microbial taxa, or between microbial taxa and host, diet, and other aspects of the environment.

Walter and colleagues argue that most such studies suffer from insufficient rigor in experimental design, inappropriate statistical analyses, and bias. In only 63% of the reviewed studies (24/38) did the researchers test to determine whether there was "dysbiosis", variously measured or defined, in the rodent model (the authors acknowledge conceptual worries about dysbiosis, discussed in Section 1 above, and define it for the purpose of their discussion just in terms of "an altered microbiome associated with a specific disease or condition as compared to a control" (p. 221)). In only 29% of the studies did researchers confirm a specific change in microbiome composition. The majority of studies did not attempt to identify a causal component of the microbiome that led to disease, and only 13% identified underlying mechanisms linked to disease. Moreover, many of the studies (84%) used a small sample size of donors and a high sample size of rodent models, inflating the effect size, which Walter and colleagues identify as "pseudoreplication." They warn that this small number of donors risks not accounting for inter-individual variability of human microbiomes. Using studies such as these to guide clinical therapy—for instance, fecal microbiota transplantation (FMT) from healthy humans to diseased humans—might cause harm if the microbiome alterations are not causal or contributory to the disease but instead are compensatory or bystander responses to disease. The authors thus recommend that researchers make a greater effort to determine which microbiome alterations are associated with pathology, use an appropriate number of donors to account for real biological variation, avoid pseudoreplication, do not pool donor samples, confirm whether microbiome engraftment was successful, and honestly discuss the limitations of animal models.

We wish to draw out a larger point, building on Walter and colleagues' critique of this work: given the extreme heterogeneity on both sides of the causal equation—that is, of both cancer as a disease and of the microbial variables in play—attention to this heterogeneity, and to context specificity of both cause and effect variables, is crucial. Arguably, to warrant extrapolation to human subjects, standards for establishing successful intervention ought to be especially strict.

Turning from studies of animal models to studies of human subjects, we consider as a case study the use of FMT in treating human cancer patients. Intuitively, it might seem that studying human patients rather than mice should lead to more direct answers to causal questions about microbiota and cancer. However, similar concerns arise here.

In a 2020 paper in *Science*, Baruch and colleagues did a phase 1 study of FMT from donor melanoma patients who responded to treatment, to recipient patients who hadn't responded to the same treatment. Advanced melanoma (melanoma that has spread to other parts of the body via

metastasis) is difficult to treat. Various therapies have been shown to temporarily slow or halt growth of metastatic tumors, but the tumors eventually progress. The treatment in question in this study, nivolumab, was an anti–PD-1 immunotherapy, a programmed cell death 1 (PD-1) receptor inhibitor. It has been shown to have "durable responses" (more on this below) with fewer adverse events, compared with chemotherapy or other cytotoxic drugs, in advanced melanoma.

The rationale for the study, according to the authors, was that the "gut microbiome has been shown to influence the response of tumors to anti–PD-1 (programmed cell death–1) immunotherapy in preclinical mouse models and observational patient cohorts." Also, "most of the patients do not respond to PD-1 blockade, and many of the partially responding patients eventually progress" (Baruch et al. 2020, p. 1). The goal, then, was to improve responses to treatment in these treatment refractory patients. The authors cited mouse FMT studies in support of this investigation. Their human study used two donors and ten recipients, and effectiveness of the intervention was measured based on a common surrogate for overall survival in immunotherapy studies, objective tumor regression (Seymour et al. 2017). The authors found that less than 1/3—three out of 10—patients responded to the FMT therapy, and only one of these three showed a "durable" response (their tumor did not grow over the duration of the study). Nonetheless, the authors' conclusions were overwhelmingly positive: "This study demonstrates that the combination of FMT from a CR [complete response to therapy] donor and reinduction of anti–PD-1 therapy in refractory metastatic melanoma patients is safe, feasible, and potentially effective" (Baruch et al. 2020, p. 6).

The suggestion that the transplanted microbiota potentially caused the improvement in cancer outcomes was only weakly supported by the evidence. The microbiota could be causal, or complicit actors, or passive bystanders with respect to the outcome. The paper itself shows only a weak association with durable response to treatment. Indeed, the authors admit that "no clear association between those taxa and clinical response to therapy was established" (p. 6), where "those taxa" refers to taxa which differed in a statistically significant way between recipients' pre- and post-treatment microbiota composition observations.

In other words, it is unclear where this study is meant to sit with respect to our first trade-off: whether whole microbiome features, or specific microbial taxa, are meant to be potentially explanatory of response to treatment. The authors appear to have both in mind. In addition to referring to the gut microbiome as a whole throughout the paper, Baruch and colleagues also focus on 16S identification of particular "beneficial" taxa associated with immune functioning. This suggests that if anything microbial is causally implicated in melanoma treatment response, it might be those taxa in particular. But none of the researchers' interventions involved culturing or otherwise isolating those taxa. So it is unclear how identifying those taxa as present, among many others, establishes that they play a causal role, given everything else going on in the intervention. Naming specific taxa only gives the appearance of a more fine-grained microbial causal story. And a causal claim about whole gut microbiomes does not become more credible, as such, by pointing out the existence of particular microbial taxa that might play a role in immune function. As a further complication regarding the microbial variable, FMTs are

commonly thought of in terms of intervening on whole gut microbiomes.[12] Yet several studies suggest that only a subset of microbes from the gut make it into the stool, and thereby into FMTs (Momozawa et al. 2011; Zmora et al. 2018).

While this study is only one of many we could have considered, it nicely illustrates that choosing to study human patients rather than mouse models does not necessarily support more robust causal claims about the microbiome and cancer. It also illustrates several reinforcements of our earlier messages. First, it is easy to confound claims about microbial causes versus complicit actors versus passive bystanders. Second, it is important to be clear about the putative microbial variable in question—is it "the gut microbiome", or just the few specific taxa identified with 16S analysis and named (typically at the genus level) as candidate causal actors regarding the outcome of interest? More clarity about the relationship between the coarse-grained (microbiome) and fine-grained (particular microbial taxa) causal claims is needed in these sorts of studies and in subsequent discussions of them. Third, when a clear causal or even associational story is lacking, findings would be more productively framed in terms of generating compelling causal hypotheses to investigate further. The authors conclude that their study demonstrates that FMT is "potentially effective" in the cancer treatment context of interest. We do not think they are saying anything false or intentionally misleading here; there is plenty of room for interpretation in "potentially." But this conclusion would arguably be better framed not in terms of a tentative causal connection, but instead in terms of proposing specific promising causal hypotheses to test further: for example, regarding the relationships between FMT, as a clinical intervention, and response to anti-PD-1 therapy in nonresponsive melanoma patients, or regarding the relationships between the specific microbial taxa identified in the study and response to anti-PD-1 therapy.

3. Explanation versus diagnosis and treatment

As in most biomedical research, the research we're concerned with here falls along a continuum from "upstream" or "basic science" questions about fundamental patterns of association, causal processes or mechanisms, to "downstream" questions about prevention, diagnosis, or treatment. Much research on the microbiome and cancer has the long term goal of preventing, diagnosing, and treating cancer. Intuitively it might seem like mechanistic understanding is a prerequisite for successful treatment development; but this is not necessarily the case. Knowing how a drug works has historically trailed the development of the drug as a treatment, sometimes by decades. There are many examples of drugs for which the mechanism is poorly understood, if not still a mystery, such as acetaminophen for pain relief (Drahl 2014), lithium for bipolar disorder (Malhi et al. 2013) and other psychiatric drugs (Ban 2006). Hargrave-Thomas and colleagues (2012) argue that as much as 35% of cancer drug discovery has been as often a matter of luck and accident as design.

[12] For example, Baruch and colleagues write that FMT "transfers the entire gut microbiota from one host to another" (2021, p. 602), and McQuade and colleagues write that "[w]ith [FMT], an entire enteral microbial ecosystem is transplanted from the donor or donors, offering multiple potential advantages over delivery of single beneficial bacteria" (2019, p. e85).

Whether the primary aim is explanation or treatment, a central strategy to avoid conflating correlation and causation is precisely intervening on some microbial variable and seeing how it effects some cancer outcome. This connects back to the issues discussed above regarding trade-off 1, the fineness of grain of the variables. We can be more fine-grained or more coarse-grained in our "wiggling" of one variable to see how it affects another. In a research context where explanation is the primary aim, it arguably makes sense to prioritize fine-grained variables. To the extent that the research context focuses purely on finding and developing viable treatments, researchers might reasonably accept more coarse-grained variables—as long as they work.[13]

So researchers might be pulled in different directions regarding the fineness of grain of the microbial and outcome variables; on this trade-off, given limited resources, most studies cannot aim to achieve explanation and treatment at once. In that sense, this is a largely pragmatic trade-off. That said, the aims of explanation and treatment are often both practically and epistemically interconnected. For instance, much of the work on humanized mice discussed above aims at developing FMT for prevention and treatment of cancer. As Elinav and colleagues (2019) write: "Paramount to the development of microbiota-based therapeutics, the next challenge in microbiome research will be to identify individual microbial species that causally affect cancer phenotypes and unravel the underlying mechanisms" (p. 371). Arguably, we can get only so far with microbiome-based cancer treatments until we have a detailed understanding of specific causes and mechanisms in play. Some microbial interventions, like FMTs, might be promising in the treatment context even if we do not as yet understand why or how the transfers are effective.

A series of studies on intratumoral microbes illustrates this trade-off between explanation and treatment, and its connection to the bigger issues at stake regarding causal attribution. Microbes are found in just about every micro-environment within our bodies, and tumors appear to be no exception (for a review of this literature, see Sholl et al. 2022). Some researchers have sought to explore whether and how the tumor microbiome affects cancer development or response to treatment.

Some studies suggest that intratumoral bacteria may play a role in promoting and preventing metastasis or modulating responses to cancer drugs (Geller et al. 2017; Pushalkar et al. 2018). While the associations in question are suggestive, it is not clear whether the bacteria involved are causal, complicit actors or bystanders. Wong-Rolle and colleagues (2021) review the literature on potential mechanistic relationships between local microbiomes and cancer (specifically lung, gut, and other cancers associated with mucosal tissues). Many of the studies they cite suggest possible microbiota associated differences in various cancer outcomes, such as mutagenesis and antitumoral immune response, but do not confirm causal relationships.

Studies seeking to establish these sorts of promising connections between local tumor microbiota and cancer often highlight potential diagnostic and therapeutic payoffs. For example, studies mentioned above propose that "microbial-targeted therapies may reduce risk in preinvasive disease," "suggest that elements of the microbiome may be useful in early diagnosis and risk stratification" (Pushalkar et al. 2018, p. 404), and "suggest that a new class of microbiome-based cancer diagnostic tools may provide substantial future value to patients" (Poore et al. 2020, p. 574). 'Suggest" is the key word to bear in mind here: while these associations are intriguing and

[13] Thanks to Jay Odenbaugh for suggesting this framing of the issues here.

worth exploring further, it is a big leap from microbiome-cancer associations to diagnostic tools and treatments, especially when extrapolating from findings about particular microbes and particular cancers.

For cancer microbiome researchers and downstream researchers hoping to develop therapeutic applications, there are big questions worth asking here, including how to ensure that the best current data are being used in developing drug or immunotherapy targets (see Sholl et al. 2022). For historians and philosophers of science, and others contributing to broader scholarly and public discussions of this work, there is the question of how to assess the promises of this research and its causal intimations. For both groups, it is worth bearing in mind the importance of avoiding overstated implications.

4. Conclusion

We have discussed three trade-offs as they arise in cancer microbiome research, argued against overstating and overinterpreting causal findings in this research, and argued for framing and interpreting some findings in terms of promising causal hypotheses to investigate further, rather than in terms of tentative causal claims. While there are clear-cut examples of infections by specific microbial taxa promoting specific cancers, such as viral infection with HPV or Hepatitis B, there are many more cases of less straightforward relationships—especially when both the microbial and outcome variables are more coarse-grained—which require further exploration.

In light of this discussion, we can return to the question of how the study of microbiome-cancer connections presents a "perfect causal storm" as suggested in the introduction. Similar trade-offs and problems with causal attribution will arise in studying the microbiome and many other diseases, especially complex ones, such as inflammatory bowel disease. So what is special about this context?[14] The cases we discussed in sections 1–3 illustrate how cancer is distinct from other diseases in a variety of respects, and so presents distinctive challenges in its intersection with microbiome research as an already especially challenging basis for causal explanations.

Cancer is a singularly heterogeneous condition. While both inflammatory bowel disease and cancer are umbrella terms for ranges of more specific conditions, the former range at least occur in the bowel. Cancer arises in tissues and organs all throughout the body, each with their own particular microenvironments, requiring careful attention to the microbial factors potentially at work locally in each such context. References in the literature to the effects of "the microbiome" or "dysbiosis" on "cancer" as a whole fail to attend to particular cancer types and subtypes, as well as particular microenvironments, particular microbial taxa, and any potential causal roles they play in a given cancer's initiation, progression, or response to treatment. Even implicitly generalizing from one cancer to another—whether regarding the causal variables in play, their relative localization, or the effectiveness of various interventions—can lead to serious harms.

Furthermore, cancers and microbiomes both exhibit great variation not only across individuals but also spatially and temporally within a given individual. Cancer exhibits many features of an evolutionary process; it consists of populations of cells that vary in genetic and phenotypic

[14] Thank you to an anonymous reviewer for encouraging us to elaborate on this question.

features which, over the course of cancer progression, can lead to changes in the distribution and dispersal of different lineages of cells in both the original tumor and in metastatic sites.[15] Different microbial factors might well play different roles at different stages. A late-stage tumor or a cancer that has been subject to treatment are not likely to be identical to the same patient's cancer at an earlier stage, whether with respect to the genetic features of the cancer cells, the microenvironment and microbial taxa found in a tumor, or any larger-scale interactions between the host's resident microbes and disease progression. Thus, attention to when and where samples of tumor features are taken, and how they are used to support causal claims, is crucial, especially where such sampling is used to make causal inferences about potential interventions. As mentioned above (Section 1.2), examples of research in this area attending to change over time on both sides of the causal equation include prospective cohort studies, where researchers follow a cohort of subjects over time and take microbiome samples before, upon, and following up on cancer diagnosis and treatment. Such studies might ultimately provide more solid support for causal claims than many of the studies we have reviewed here.

In sum, the enormous context dependence and heterogeneity of cancer, as well as its distinctive dynamics, should make researchers on cancer and the microbiome especially cautious along all of the axes of causal attribution discussed in this paper.

Having recommended great caution and precision in formulating causal hypotheses about the microbiome and cancer, we should note in closing that sometimes information about general patterns of association might be valuable, as long as it is explicitly framed as such and not more. To this point, it is worth returning to the exchange between Lynch and colleagues (2019, 2020) and Attah and colleagues (2020) discussed in Section 1, regarding the preferability of more coarse-grained versus fine-grained microbial explanatory variables. We agree with Attah and colleagues that different interests dictate different choices of causal variable; moreover, we grant that other pragmatic considerations, such as ease or availability of an intervention, legitimately influence the choice of a more fine-grained or coarse-grained variable.

As DiMarco (2021) argues, in the context of epidemiology and public health, we should prefer black-boxing when filling in the details might "actively mislead us with respect to the stability of a cause" (p. 11). She is concerned primarily about black-boxing steps in a causal chain in public health contexts, whereas we are concerned more with drawing lines around the putative cause itself in a targeted medical intervention. But an analogous point can be made here: Knowing that an intervention works can come prior to any detailed knowledge of the mechanism or specific causal pathway involved. We agree with Lynch and colleagues (2020) that we should be careful about black-boxing in medicine, but we also grant (with DiMarco 2021) that despite good intentions in making causal stories more detailed, there might sometimes be epistemic reasons to prefer black-box explanations. This is especially the case when the research agenda puts developing treatments that work in the foreground, and deeper causal or mechanistic explanation in the background, as discussed in Section 3. The key—connecting this to our other cautionary recommendations—is to explicitly acknowledge the black-boxing, and which step(s) in the

[15] We grant that the similarity to evolving populations of free-living cells is a matter of degree, not kind, and there are various limitations to the comparison (for discussion see, e.g., Germain 2012; Lean and Plutynski 2016; Germain and Laplane 2017; Okasha 2021).

causal story it applies to, so that if and when treatment fails, we can investigate and better understand why.

Several take-home points are worth emphasizing in closing. The first is the importance of transparency. In framing causal stories where two already causally complex targets of investigation are coming together, researchers ought to be especially clear about which microbial variable(s) they see themselves as intervening on; refrain from ever suggesting they are intervening on whole microbiomes when they are not (see Lynch et al. 2019); and similarly refrain from causally implicating specific taxa when the intervention at stake was in fact more coarse-grained (recall our discussion of Baruch and colleagues (2020)). Researchers ought to be clear about what they have shown, distinguish what they have actually shown from tantalizing possibilities, and avoid overstating the causal implications of their findings. In the interest of correct causal attribution, it is important to avoid reporting findings about "the microbiome" when they were in fact about particular microbial taxa or localized microbial communities (for example, in a tumor), and similarly to avoid reporting findings as generically about "cancer" when they were in fact about a specific cancer type or responses in patients with a specific cancer to a specific treatment.

This is just as much a cautionary take-home point for historians and philosophers of science engaging with this research area. We have discussed trends of researchers overstating the causal implications of their research; a cynical read on this regards larger issues in the sociology of science around incentives to publish high-impact results. Such incentive structures might or might not drive some of the issues we raised in this paper. In any case, it is all the more reason to stress that historians and philosophers of science should maintain a critical eye with respect to these matters of causal attribution.

Second, as we suggested at several points in our discussions of trade-offs, at least some current research on the microbiome and cancer would be more productively framed in terms of answering the question: "Which specific causal hypothesis can we test next, and how should we frame the microbial variable on the coarse/fine-grained spectrum, given our research aims?" This would be preferable to framing findings as even tentative causal stories, where there is association at best, or because the causal variable is ambiguously characterized, or both. While 'exploratory research' might be somewhat of a derogatory term amongst many scientists, a pocket of literature in philosophy of science has highlighted the value of exploratory experiments (and models) as means to generate productive hypotheses to test when forging new empirical and theoretical territory, especially in young research areas (see, e.g., Steinle 1997, Franklin-Hall 2005). Such caution is especially warranted in contexts such as cancer research, where data require constant updating, and data travel quickly between upstream and downstream contexts in ways that could lead to serious harm to patients.

Cancer research is not a young field, but its intersection with microbiome research is. We do not want to suggest that the whole field of cancer microbiome research would be best thought of in exploratory terms. But we do think this research area, and philosophical examinations of it, could benefit from a reminder that sometimes it is valuable to focus on hypothesis generation and set aside the aim of explicit hypothesis testing, at least for the moment. In other words: when the microbial variable in question is so poorly understood as to be impossible to specify—is it a

microbial community-level feature? Some particular taxon or taxa?—don't bury that causal ambiguity behind loose suggestions of a compelling causal possibility or claims about the microbiome as a whole being causal. Instead, a more productive avenue towards explanations and treatments is to generate specific causal hypotheses to test and to be as clear as possible about their parameters, especially on trade-offs 1 and 3.

Acknowledgments

We thank Helena Copsey for research assistance. We are also grateful to Mark Bedau, Kendall Clements, Avram Hiller, David Kelley, Cole McArthur, Liz Mallott, John Matthewson, Jay Odenbaugh, Maureen O'Malley, James Rowarth, Jacqueline Wallis, the audience at ISHPSSB 2021, and two anonymous reviewers for valuable discussions and feedback on drafts of this paper.

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