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REVIEW

Can societal and ethical implications of precision microbiome engineering be applied to the built environment? A systematic review of the literature

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Abstract
The goal of engineering the microbiome of the built environment is to create places and spaces that are better for human health. Like other emerging technologies, engineering the microbiome of the built environment may bring considerable benefits but there has been a lack of exploration on its societal implication and how to engineer in an ethical way. To date, this topic area has also not been pulled together into a singular study for any systematic review or analysis. This study fills this gap by providing the first a systematic review of societal and ethical implications of engineering microbiomes and the application of this knowledge to engineering the microbiome of the built environment. To organize and guide our analysis, we invoked four major ethical principles (individual good/non-maleficence, collective good/beneficence, autonomy, and justice) as a framework for characterizing and categorizing 15 distinct themes that emerged from the literature. We argue that these different themes can be used to explain and predict the social and ethical implications of engineering the microbiome of the built environment that if addressed adequately can help to improve public health as this field further develops at global scales.

Keywords Microbiome · Built environment · Societal and ethical implications · Systematic review

1 Introduction

Precision microbiome engineering is a rapidly evolving field at the intersection of microbiology, genomics, and engineering, which focuses on the possibility of manipulating the microbial communities inhabiting various environments, including the human body, to improve health outcomes. This technology aims to selectively modify the composition and function of microbial communities to achieve specific therapeutic effects, such as treating metabolic disorders, infectious diseases, and cancer (Liang et al. 2019). The ability to engineer microbiomes with precision offers significant promise for developing targeted and personalized therapies, as well as for enhancing our understanding of the complex interactions between microorganisms and their environment (Langdon et al. 2016).

The built environment (BE) of human-made and adjacent structures contains diverse microbial populations (viruses, bacteria, unicellular eukaryotes, and fungi). Humans have extensive interactions with the microbiome of the built environment (MoBE) via air circulation, water flowing in plumbing, and the surfaces of from the most accessible touched objects (Li et al. 2021). These microbial communities and their metabolites have been implied to cause (or exacerbate) and prevent (or mitigate) human disease through various exposure pathways: inhalation, ingestion, dermal contact, etc. Understanding this process is of growing importance in industrialized societies where people spend 90% of their time indoors (Klepeis et al. 2001).

The chief factors determining the MoBE are building layout which influences how occupant-associated

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microbiome are dispersed in the BE, sunlight exposure, ventilation, temperature, moisture, building materials, and plumbing systems (Hathway et al. 2011; Li et al. 2021). These factors drive the development of new technologies to address MoBE composition, such as using antimicrobial building materials, advanced HVAC systems that mitigate moisture and control temperature, building design that maximizes the use of sunlight to control microbial growth, premise plumbing systems that minimize pathogen growth (e.g., *Legionella, Mycobacterium* sp.), and cleaning and disinfection strategies (e.g., UV radiation). Additional ideas include the use of indoors plants to introduce more beneficial microbes (Li et al. 2021). However, all these strategies must be taken with caution because they do not consider the capacity of pathogenic microbes to evolve resistance (Graves 2021).

Alongside the technical nuances of the MoBE, this emerging field also raises significant societal, ethical, safety and governance concerns, such as privacy, informed consent, the racialization of spaces, and equitable management of the MoBE (De Wolfe et al. 2021; Franzosa et al. 2015; Robinson et al. 2022; Shamarina et al. 2017). As the field of precision microbiome engineering for the MoBE continues to advance, it will be important to carefully consider the implications of this technology and to develop appropriate governance frameworks to ensure its responsible development and equitable use (Nestle et al. 2019). Such investigations will be crucial for future technological development and risk communication initiatives and can help to promote appropriate public engagement.

This paper provides the first systematic review of the published literature on the societal and ethical implications (SEI) of precision microbiome engineering research and applies it to the MoBE. There has been little explicit research on SEI within the context of the MoBE with the SEI literature instead focusing on the microbiome in general with occasional references to the MoBE. To address the deficit on SEI within the MoBE, we provide an overview of SEI within precision microbiome engineering in general and apply it to the context of the MoBE. This review intends to enhance dialogue in this emerging field of the MoBE and provide a stronger basis of understanding that can empower responsible research and innovation, anticipatory governance, and upstream communication of risks and benefits. Ultimately, the aim is to ensure that the state-of-the-science of precision microbiome engineering of the MoBE is developed with appropriate social and ethical investigation to guarantee equitable access, choice, and use. Equitable use is particularly significant here, as many of the health risks associated with microbiome dysbiosis (e.g., asthma, autoimmune disease, infections during infancy, and mental health) differentially impact poor, black, and brown Americans (Amato et al. 2021).

Prior to detailing the method of our sample selection, this review first 'unpacks' the terms associated with precision microbiome engineering. Following this introduction to the scope and methods, we discuss the current state of understanding of SEI in precision microbiome engineering and propose how this information can be applied to the MoBE.

2 Terminology

This section outlines the different terms that informed our understanding of the BE, precision microbiome engineering, SEI, and the ethical principles used to organize SEI. These terms informed the development of our methods from the search parameters we used to the criteria we created for determining which articles to include in our systematic review.

2.1 Precision microbiome engineering, the built environment, and implications for public health

Defining the BE and precision microbiome engineering was based on the standards set by the NASEM (2017) Report "Microbiomes of the Built Environment: A Research Agenda for Indoor Microbiology, Human Health, and Buildings." This report was used since it was a comprehensive review of previous natural sciences literature on the MoBE and likely influenced literature since its publication. In this report, the BE was defined as various types of structures and related elements that are "designed, built, and managed by humans" (NASEM 2016, p. 1) and the MoBE refer to "microorganisms (bacteria, archaea, eukaryotes, and viruses), their genomes (i.e., genes), and the surrounding environmental conditions" (NASEM 2017, p. 294). In sum, for our systematic review, the MoBE is understood as microbiomes found in human-made structures and adjacent spaces common to urban centers, like green spaces, residential, commercial, mixed-use buildings, and hospitals. Left out of this definition and the focus of this review are structures and spaces not as common to urban centers and managed by humans like agricultural land where there are active discussions on modifying their microbiomes that carry with them their own unique SEI (Sergaki et al. 2018).

For the purposes of our systematic review, we defined precision microbiome engineering based upon NASEM's (2017) definition of MoBE research. Precision microbiome engineering is defined as approaches that lead to the prevention of infectious agents' colonization and promotion of beneficial microorganisms' proliferation in the MoBE. This type of definition captures two of our four ethical principles (beneficence and non-maleficence) that we discuss more later and reflects much of the focus of engineering the MoBE which is to increase benefits and/or reduce harm.

Many recent advances demonstrate potential benefits of precision microbiome engineering on public health and has widespread implications of understanding factors that contribute to disease prevalence and progression and treatment (Neish 2009; Postler and Ghosh 2017). For instance, recent evaluation of gut microbiota has led to new hypotheses regarding the influence of urbanization on gut microbiota and inflammatory bowel disease (Zuo et al. 2018).

While these advances proffer potential revolutionary benefits to public health and society, guiding the development of this field to provide safe and equitable solutions will require not only technical soundness but also consideration of a variety of SEI as we detail below.

2.2 Societal and ethical implications

We define SEI as questions of integrity, ownership, risk, health, governance, fairness, equity, justice, and power in social relationships (Lewenstein 2006). SEI can take many different forms and this can be seen later in the many different categories we used to group articles that discussed SEI within the MoBE. With this definition of SEI in mind, the acceptance and potential deployment of new technologies like precision microbiome engineering are influenced by the values-based assessments and decisions of the broader public. Therefore, developers need to consider the potential reasons why diverse public domains may be concerned or opposed to the application of a new technology. Failure to do so could lead to a loss of public support for the field and derail opportunities to actualize potential technological benefits at global scales (NASEM 2016).

The societal implications of biotechnology are also influenced by cultural norms and societal taboos, such as cultural symbols, social values, and dominant media frames. Pauwels (2013) found that values and trust significantly impact public perceptions of biotechnology. This can be seen in genetically modified crops where a lack of trust developed due to the need for non-government organizations to push for federal regulations through court cases and media campaigns (Kuzma 2022). Like the issues with first-generation biotech crops, Kuzma and Cummings (2021) also observed critical views of biotechnology among stakeholder groups, where cultural beliefs influence opinions on biotechnology and gene editing. Cummings and Peters (2022) and Dahlstrom et al. (2022) found that social values, antecedent value dispositions, and media frames likely influence how the US public views novel agrifood technologies, such as gene-edited crops. It is crucial to understand and respect the various risk cultures within and across societies, which are moral views and values regarding the perceived risks and opportunities yielded by an emerging technology, where biotechnologies will be deployed. Upstream involvement early in the engineering of the MoBE will be needed to understand and respect perceived risks of this biotechnology.

2.3 Literature on ethical principles

We chose a bioethics framework to describe the ethical issues associated with precision microbiome engineering in the BE, as a bioethics-based framework was suggested recently by the NASEM (2021) for governance of emerging technologies (Mathews et al. 2022) and also fits the ethical issues surrounding governance of genetically modified organisms that come in contact with humans (e.g., Kuzma & Besley 2008). In the development of precision microbiome engineering, many of the ethical considerations span four key principles of bioethics: individual good/non-maleficence, collective good/beneficence, autonomy, and justice (Beauchamp & Childress 2013; Mathews et al. 2022; Trump et al. 2023). Individual good/non-maleficence prohibits intentionally causing harm, including harm from negligence and collective good/beneficence entails the duty to "do good." Autonomy recognizes individual rights and the importance of free will. Justice is crucial for ensuring a fair distribution of benefits and costs across all individuals affected. Justice has become increasingly important to decision-makers in planning and technology implementation. For example, opponents of genetically modified crops argue that the benefits primarily accrue to producers, while the risks fall mainly on consumers (Kuzma & Besley 2008; Cummings et al. 2023). Equitable biotechnology processes should aim to have the same population bear both risks and benefits. (Beauchamp & Childress 2013; Kuzma & Besley 2008; Jasanoff 2016). Lastly, we want to acknowledge that this is a biomedical ethics lens which means that people are prioritized over the MoBE. There are multiple different other ethical lenses, like environmental ethics, engineering ethics, and post-human ethics that should be considered in future research (Harris Jr. et al. 1996; MacCormack 2012; Rolston 1987). Environmental ethics would require researchers to consider how influencing the MoBE affects the people, plants, and animals that exist in a shared space (Rolston 1987). Engineering ethics asks that as we engineer the MoBE to consider a code of ethics that can be used to judge our actions beyond only reducing or preventing harm (Harris Jr. et al. 1996). Lastly, post-humanism challenges us to consider the impact of a human-centric viewpoint and to consider the perspectives of other non-humans intertwined in the MoBE (MacCormack 2012).

2.4 Safety-by-design and anticipatory governance of precision microbiome engineering (PME)

A thorough review of the SEI of precision microbiome engineering can inform safety-by-design and anticipatory governance approaches that adequately prepare decision-makers for the likely benefits and risks of this emerging field. A safety-by-design approach was suggested two decades ago for the deployment of genetically modified organisms (Kapuscinski et al. 2003). More recently, Trump et al. (2023) proposed a safety-by-design process for biotechnology development which implored examination of the SEI of the biotechnology innovation process along with explicit and transparent evaluation of a developing technology's safety, security, and regulatory standing. They argue that safety-by-design is a proactive approach that aims to eliminate potential hazards associated with a technology at the earliest stages of its development through technical or procedural measures. This approach involves ongoing evaluation of the technology's physical characteristics and safety as well as the SEI of its development and use to identify and mitigate any risks to human health or the environment. Therefore, the safety-by-design framework extends beyond technical safety standards, encompassing social, and ethical considerations as well which can more readily account for broader public concerns and support for their products. Developers can prevent unacceptable outcomes or products by proactively assessing the SEI of a technology during its early stages of development. This approach can streamline the timeline from innovation to commercialization, mitigate downstream hazards, reduce the need for expensive risk transfer requirements, such as insurance, and build public confidence by demonstrating that products undergo rigorous testing and evaluation against stringent social and ethical benchmarks before entering the market. Thus, safety-by-design encourages biotechnology developers to consider not only technical safety standards, but also the potential SEI of their products, ultimately promoting responsible development and use of biotechnology.

Anticipatory governance uses available information to make flexible and responsive decisions regarding the development and regulation of new technologies, aiming to foresee health and environmental impact and the SEI of emerging technologies upstream of technology development and then integrate these assessments into the technological development (Guston 2014; Guston and Sarewitz 2020). Anticipatory governance has been used in the fields of emerging nanotechnologies and biotechnologies (Cummings & Kuzma 2017; Kuzma et al. 2008; Kuzma & Tanji 2010; Guston 2014). Upstream identification of SEI can improve technology development through real-time technology assessment where the concerns identified upstream can be considered in the development of the technology itself (Guston and Sarewitz 2020). It can also be used to improve the mitigation of potential health and environmental risk by altering the course of the technology to reduce such risks prior to presentation to regulatory authorities or market release (Kuzma et al. 2008). Although this corpus of literature is not wholly generalizable or static, it serves as the first bastion of inquiry and discussion in this area and may aid in the development of anticipatory risk processes for precision microbiome engineering, particularly in the face of high uncertainty regarding its feasibility and impacts.

The focus of this study is therefore to examine and identify the primary SEI of precision microbiome engineering research by conducting a review of existing literature. The study emphasizes the significance of considering these implications in the development of technology and safety-by-design and anticipatory governance initiatives to ensure equitable access, choice, and safe utilization of the technology. Overall, we contend that by comprehensively understanding the SEI of this technology, decision-makers and funders can prioritize research areas that address public concerns about potential public health and societal hazards, while researchers and developers can ensure that their work is conducted responsibly and has greater chance of public acceptance in the market.

3 Methods

This review article focuses on the SEI of precision microbiome engineering with an application of SEI from general precision microbiome engineer to the MoBE. The inclusion criteria for studies were limited to those that were published by academic or professional groups. The search did not consider gray literature, conference proceedings, or individual publications. Our review of the literature progressed from a gathering of literature known to the authors, to a systematic review, and to ending with a forward and backward citation search. We initially intended to only include literature focused on the SEI of the MoBE, but we found only one article out of 83 that did so between our preliminary literature review, systematic review, and forward and backwards citation search (Shamarina et al. 2017). Shamarina et al. (2017) referred to the built environment in its abstract and discussed the built environment throughout the article. Instead, we found most SEI articles either did not refer to the MoBE at all (59/83 final articles) or only discussed it within a more general discussion of SEI within precision microbiome engineering (23/83 final articles). Articles that did make any reference to the MoBE were identified using key terms, like "urban" or "built environment." Due to these findings, we changed our exclusion criteria to include SEI of precision microbiome engineering in general if the literature could be applied to the MoBE. For this reason, articles that discussed the SEI of precision microbiome engineering that could not be applied to the MoBE were not in included in our final sample and analysis, while generalizable SEI issues like privacy or ownership of microbes were included in our final sample and analysis. The following subsections describe the process that resulted in the final selection of studies for this review. This review article followed the PRISMA 2020 statement (Page et al. 2021).

3.1 Preliminary literature review

Initial literature was identified based on the authors' knowledge of past publications and non-systematic searches across Web of Science and Google Scholar. This preliminary review identified 21 articles potential that discussed the SEI of precision microbiome engineering, but only one of the initial 21 articles focused on SEI within the context of the MoBE. These initial articles were used to help develop the search parameters described below. At this point, in the systematic review the authors had intended to still only study articles that discussed the built environment in detail.

3.2 Search parameters

Retrieval of articles was conducted by one researcher on January 5th, 2023 through Web of Science with a date range from 2000 through 2022. The following search parameters were used:

> (microbiome*) AND (indoor* OR built OR building*) AND (Risk* OR SEI OR Societal OR Ethical OR Implication* OR Environment* OR Race* OR Racial OR Ethnicity OR Ethnicities OR Gender* OR Indigenous OR Socio-economic OR Cultural OR Privacy OR Consent OR Social OR Economic OR Responsible OR Responsibility OR Equity OR Equities OR Legal OR Law* OR Policy OR Policies OR Regulation* OR Governance OR Government* OR Proxy OR Proxies OR Ghost* OR Urban OR Rural OR Justice)

These search parameters were developed based on a preliminary literature review, consultation between research librarians and authors, and preliminary searches through Web of Science. The terms (microbial OR microbiology OR microorganism* OR microbe*) AND (culture*) were removed from our original search parameters due to them resulting in 9,083 off-target results, such as articles discussing how to culture microbiomes. The final set of search parameters resulted in a total of 1,314 journal articles. At this point, in the systematic review the authors had intended to still only study articles that discussed the built environment in detail.

3.3 Sample selection

One author initially separated the 1,314 journal articles into those worth investigating further or not based on title and abstract and then later by the content of the article if a decision could not be made based on the title and abstract alone. The author found quickly that most articles that discussed the SEI of precision microbiome engineering, while containing the words "indoor*" or "built" or "building*" did not discuss the MoBE in any great detail. Instead, these articles made a reference to the MoBE once or twice within a more general context about the SEI of precision microbiome engineering. It was at this point the authors designed to change the exclusion criteria from only articles discussing the MoBE in great detail to SEI articles about precision microbiome engineering that could be applied to the MoBE. Therefore, articles were considered for inclusion in the final review if they referenced societal and/or ethical implications of precision microbiome engineering that could be applied to the MoBE. This initial screening process resulted in 8 journal articles for analysis that were not found previously and 3 duplicates from the preliminary literature review were found. Of our initial 21 articles, 18 were missing from the systematic review. This was likely due to these articles not containing the keywords "indoor*" or "built" or "building*." These misses were considered acceptable since the original intent was to only use articles that discussed the built environment before the authors pivoted to a more general focus on societal and ethical implications of precision microbiome engineering that could be applied to the MoBE. At this point, 29 potential articles were identified for analysis between the preliminary literature review (21) and the systematic review (8).

Based on the results of the systematic review, a forward and backward citation search was conducted using Web of Science in March 2023. This was done to account for the change in our exclusion criteria from focusing on only articles discussing the SEI of the MoBE to focusing on SEI articles that could be applied to the MoBE. The forward citation was conducted first using the 26 articles that had been identified so far through the initial literature review and Web of Science search. 128 new articles were identified for inclusion, but after screening only 48 new articles were kept from the forward citation search. These 68 articles were then used in the backwards citation search. 2000 was determined to be the cut-off date for the backward citation search based on when microbiome articles started to grow in number (Ahmed et al., 2022). During the backward citation search 40 new articles were identified for inclusion, but after screening only 35 articles were kept from the backward citation search. The final result of the different search strategies was a total of 99 journal articles with some articles being published in 2023.

A final screening of the sample was conducted by one researcher where each article was reviewed in full before data analysis to ensure it discussed SEI of precision microbiome engineering in a substantive way that could be applied to the MoBE. One article was excluded because it was not a peer-reviewed journal article and

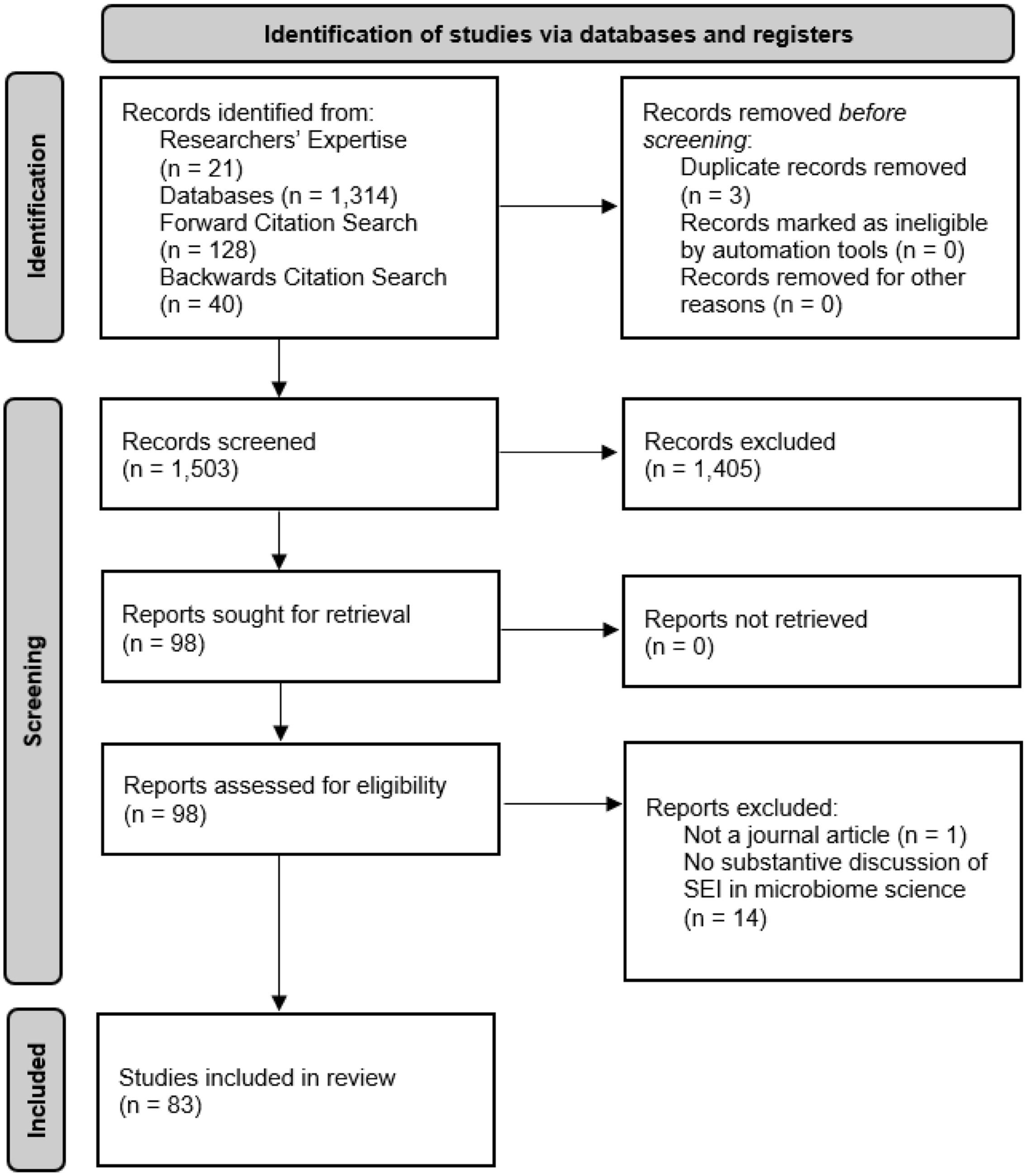

Fig. 1 PRISMA flowchart. "Researchers expertise" refers to articles found during the preliminary literature review

14 other articles were excluded because they were not a substantive discussion of the societal or ethical implications of microbiome science or engineering that could be applied to the MoBE. The final set of articles for data analysis was left at 83 peer-reviewed, journal articles. Figure 1 provides a visual overview of the entire search and selection process for this review article.

3.4 Data analysis

Data analysis was performed through an iterative, inductive process. One coder began by reading articles and coding sections based upon keywords found within the sections that were coded. The size of codes varied between a couple sentences, a paragraph, or paragraphs depending upon how

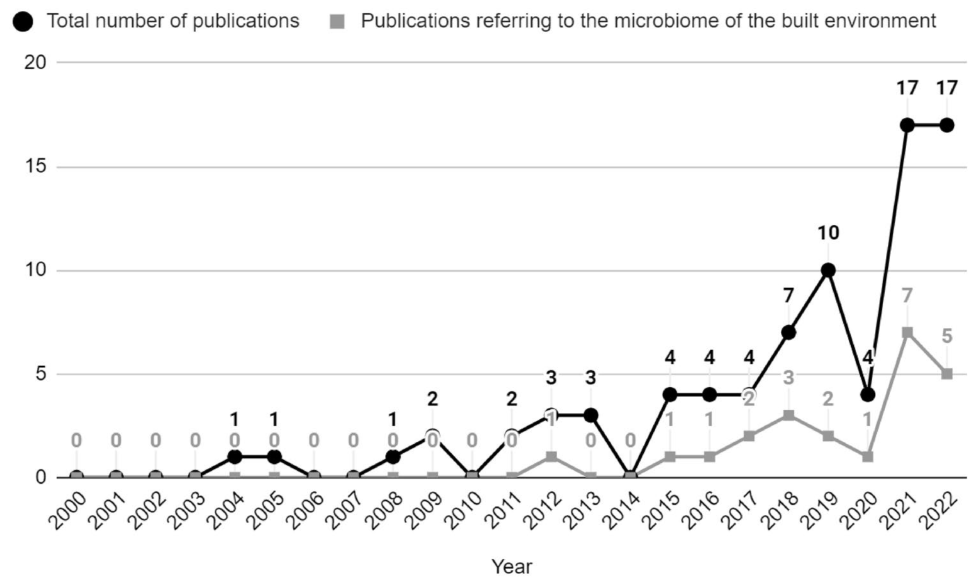

Fig. 2 Publications of articles relevant to the societal and ethical implications of engineering the microbiome of the built environment

much was needed to understand the context of the code. These initial codes were based on keywords used within the texts, such as references to justice and privacy. As more and more articles were coded for, new codes were only created when they could not fit any of the previously created codes. Articles could contain multiple different codes and certain sections of text could be coded multiple times if they referred to multiple different kinds of SEI. After all 83 articles were coded for, there was an initial total of 31 different codes.[1] After consultation between authors, the total number of codes was reduced to 20 different codes. This was an iterative process where the authors met multiple times to review the current set of codes and matched sets of codes together to form cohesive themes. How these 20 codes were applied, ordered, and used to inform our understanding of the SEI of precision microbiome engineering applied to the MoBE is explained in our results and discussion sections. 19 of our codes were used to frame our results while the last remaining code helped inform our discussion section. The reason for this separation was that our final code contained information about suggested next steps and solutions to the SEI of precision microbiome engineering that could be applied to the MoBE.

4 Results

Three kinds of articles emerged in our sample. First there were articles that could be generalized to the MoBE without referring to it. Second there were articles that referred to the MoBE in passing through the use of keywords like "urban" or "built environment" in a generalized discussion about different environments. Third, there was an article that focused explicitly on the built environment in its entirety which could be seen by referring to the built environment in its abstract and the paper itself focusing exclusively on urban environments. As a result, there are a minority of SEI studies that refer to the MoBE directly. Subsequently, discussions about the specific SEI of the MoBE are still developing with most conversations transferring generalizable elements of SEI issues like privacy and seeing how they apply to the MoBE.

There are two main subsections for our results. First, we review the composition and primary characteristics of the sample. Second, we discuss our four ethical principles and 15 themes that are connected to one or more ethical principles.

4.1 Sample composition

The final composition of our sample was 83 articles. 59 of these 83 articles were generalizable enough to apply to the MoBE while not referring to it directly (71%). 23 of these 83 articles referred to the MoBE and one of 83 discussed in detail the MoBE (29%). Figure 2 below depicts the rate of publication for both all the articles in our final sample and the ones that directly referred to or explicitly focused on the MoBE. Three articles from 2023 were kept in our final sample, but not included in Fig. 2 to not give an inaccurate count of publications for 2023.

As can be seen in Fig. 2, SEI articles applicable to the MoBE started appearing in 2004, but the first direct reference to the MoBE did not appear until 2012. This is likely due to the MoBE being a more nascent area compared to general precision microbiome engineering. As time has

[1] Our original 31 codes can be found in the appendix.

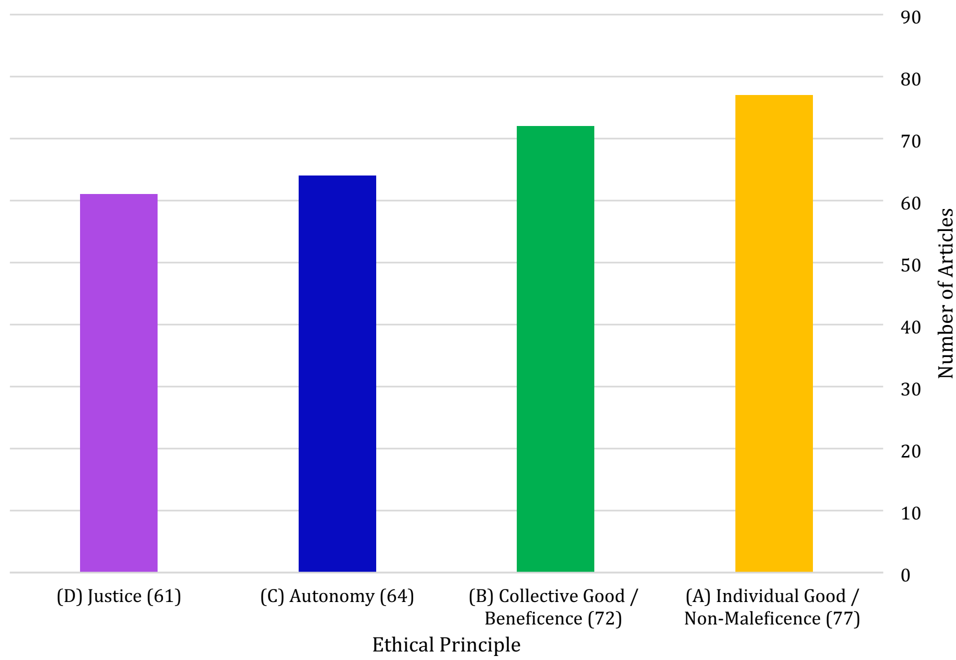

Fig. 3 Prevalence of ethical principles across our sample of 83 articles. This bar chart shows how often each ethical principle is found across our sample. To distinguish each ethical principle we created a four-letter, color-coded system, **A** (yellow) for individual good/non-maleficence, **B** (green) for collective good/beneficence, **C** (blue) for autonomy, and **D** (purple) for justice. This shows that there was some slight variation in preference for ethical principles as **A** individual good/non-maleficence appeared in 77 of 83 articles versus **D** justice which was in 61 of 83 articles

progressed, general SEI articles relevant to the MoBE have become more common and so have publications that reference the MoBE. For example, in the last two years 34 of our 83 total articles were published (41%). At the same time, 12 of our 24 articles referring to the MoBE were published in the last two years (50%). We believe that both trends will continue upward with the MoBE becoming more common as it gains more attention.

4.2 Ethical principles and themes

The four ethical principles of autonomy, justice, collective good/beneficence, and individual good/non-maleficence acted as our parent codes that all our 15 themes could fall under. This hierarchy of four ethical principles and 15 themes was adapted from the ethical framework developed in Mathews et al. (2022) and endorsed by the NASEM. Figure 3 depicts our extended ethical framework inspired from Mathews et al. (2022).

Mathews et al. (2022) ethical framework is made of three tiers with the top tier being the most abstract and the bottom tier being most specific. The top tier is ethical principles based on bioethics and philosophy literature. The middle tier are policy goals that list both procedures and desired outcomes for these policies. The middle tier is intended to ensure that the ethical principles in the top tier are put into practice. The bottom tier are policy tools that enable the policy goals in the middle tier to succeed.

In the following subsections, we go into detail about each of our ethical principles and themes. To help visualize the prevalence of our different ethical principles and themes, Figs. 3, 4, and 5 are created. Figure 3 denotes the prevalence of each of our four ethical principles across our sample of 83 articles. Figure 4 shows the ratio of our ethical principles across all our 83 articles. Together, these visualizations show that most of our sample engaged with 2 or more different ethical principles. Lastly, Fig. 5 shows how many total articles engaged with each theme and subsequently how often

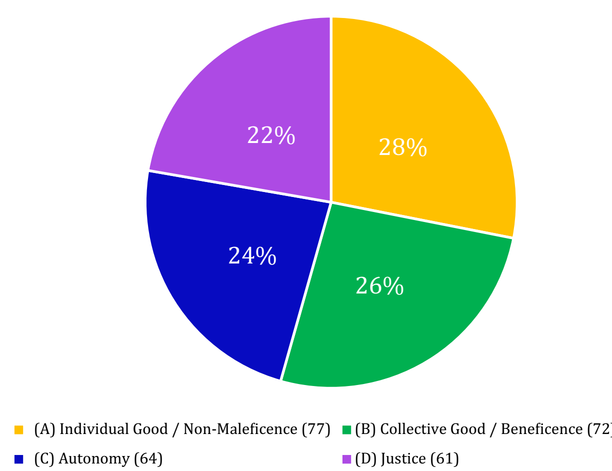

Fig. 4 Ratio of ethical principles across our sample of 83 articles. This pie graph shows the ratio of how much each ethical principle could be found across our sample. To distinguish each ethical principle we created a four-letter, color-coded system, **A** (yellow) for individual good/non-maleficence, **B** (green) for collective good/beneficence, **C** (blue) for autonomy, and **D** (purple) for justice. This shows that no one ethical principle strongly dominated discussions on the societal and ethical implications of engineering the MoBE within our sample

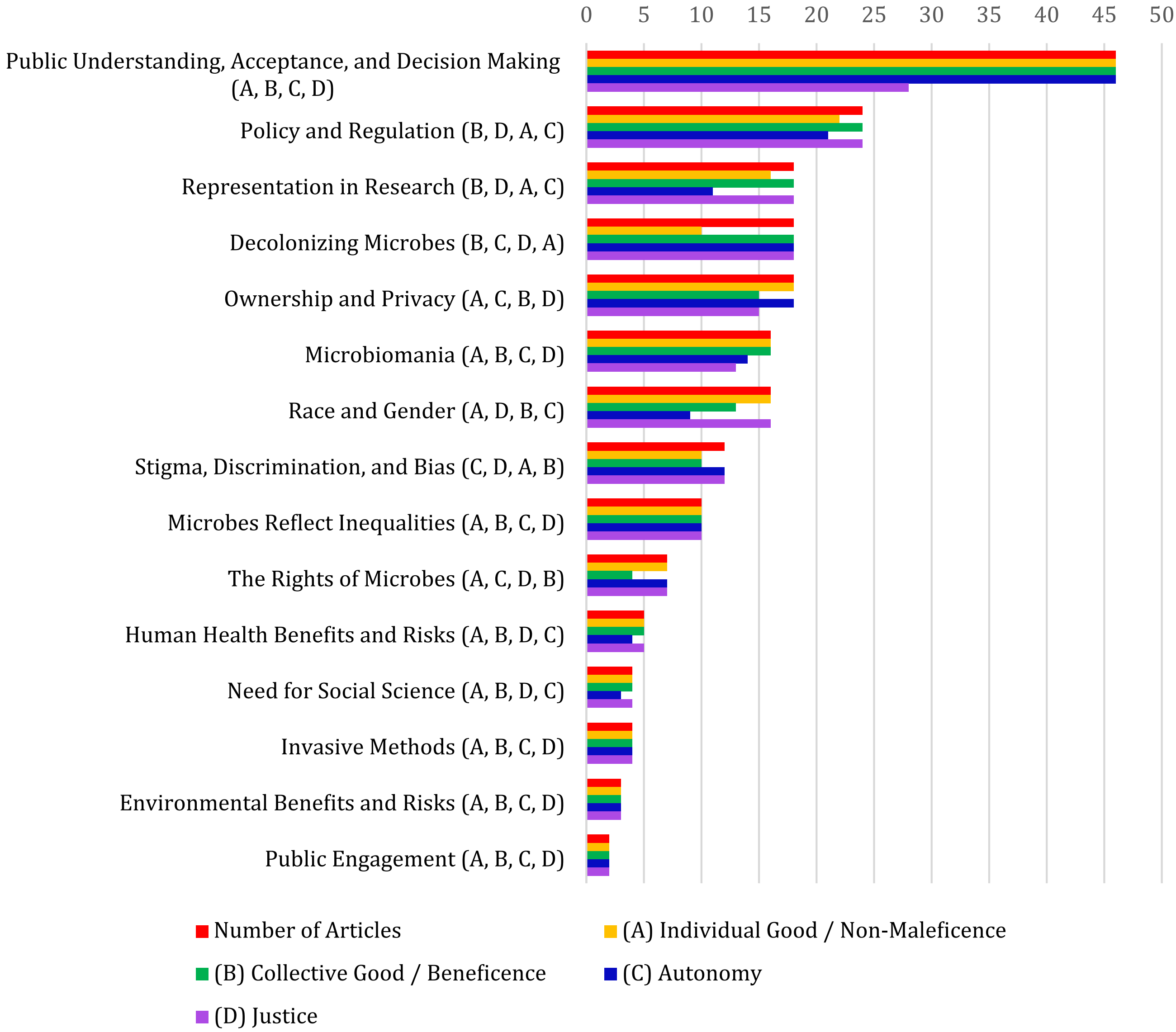

Fig. 5 Prevalence of themes and ethical principles within themes based on our sample of 83 articles. This bar chart shows the prevalence of each of our themes and how often each ethical principle appeared in each theme. All of our themes included all four different ethical principles to different degrees. To denote each ethical principle and the degree to which they applied to each theme we created a four-letter, color-coded system to mark our themes. **A** (yellow) for individual good/non-maleficence, **B** (green) for collective good/beneficence, **C** (blue) for autonomy, and **D** (purple) for justice. The order of the letters listed by each theme denotes how much each ethical principle applies to that theme. This order was based on how many of the final articles for a theme contained a reference to one or more of our four ethical principles

each article in a theme contained references to an ethical principle.

The four ethical principles are discussed first in order of prevalence as seen in Fig. 3. Following the ethical principles our 15 themes are discussed also in order of prevalence as seen in Fig. 5. For ease of understanding, each ethical principle has been assigned a letter and color: "A" (yellow) for individual good/non-maleficence, "B" (green) for collective good/beneficence, "C" (blue) for autonomy, and "D" (purple) for justice.

4.2.1 Individual good/non-maleficence (A)

Individual good/non-maleficence is defined by prohibiting intentionally caused harm which include negligence (Beauchamp & Childress 2013; Mathews et al. 2022; Trump et al.

2023). 77 of our 83 articles referred to individual good/non-maleficence and authors who discussed individual good/non-maleficence invoked it in several different ways. The following are a set of examples from that showcase some of the different ways individual good/non-maleficence was brought up.

One common thread was obligating researchers to not do harm in different ways. O'Doherty et al. (2016, p. 415) wrote, "We argue that future research needs to consider an obligation to our common microbial environment and the stewardship of the shared microbiome." In this case, researchers called for an obligation to anticipate and think ahead so that microbiomes could be preserved. This obligation leads some authors like Chuong et al. (2017) to consider when researchers may do more harm than good through misguided obligations. This can be seen when Chuong et al. (2017, p. 7) writes the following, "More controversial is the issue of whether participants should receive feedback on their individual data." Here the authors engaged in a debate of whether more harm could be caused by providing individuals with their data without certainty of what it means. Uncertainty around what microbiomes exactly mean for a person's health will likely be just as hard when studying the MoBE due to the complexity of understanding and managing the BE.

Another thread was authors pointing out current holes in legal and regulatory systems around microbiome research. For example, Knoppers et al. (2021, p. 562) wrote, "anti-discrimination policies tailored specifically to the context of genetics may not provide legal protection against potential misuses of individual epigenetic or microbiomic information." Here, authors argued that current systems meant to protect people from genetic discrimination are unlikely to provide the same kind of protection for people based on their microbiomes. Bapteste et al. (2021) develops this argument further by considering if microbiomes themselves can be individuals that hold rights to not be harmed. This can be seen when Bapteste et al. (2021, pp. 11) wrote, "A rethinking of the definitions of individuals appears also necessary to determine which individuals should be granted new rights."

4.2.2 Collective good/beneficence (B)

Collective good/beneficence is defined by the duty to "do good" (Beauchamp & Childress 2013; Mathews et al. 2022; Trump et al. 2023). 72 of our 83 articles referred to collective good/beneficence and authors discussed collective good/beneficence in one of two ways: good that researchers could do for others or good that could be done for the collective.

Different authors wrote about how researchers could do good in different ways, but one prevalent aspect was authors suggesting ways for researchers to do effective science communication. For example, Yeo et al. (2023, p. 72) argues for the use of humor in nuanced ways to communicate microbiome research when they wrote, "Our results provide compelling evidence that choices of humor types matter when it comes to communicating scientific topics." Similar to humor, disgust came up in multiple articles as a point to consider in science communication. Yeo et al. (2019) and Tybur et al. (2009) wrote about how microbes may invoke disgust and Yeo et al. (2019) wrote about how to properly communicate microbes with disgust in mind. When looking at specifically the MoBE though Greenhough et al. (2018, p. 7) found this idea of disgusting microbes missing, instead writing "We might instinctively allocate germs to a similar realm as other 'unwanted' or 'monstrous critters' which evoke disgust, horror, and killing (Davies, 2013; Ginn et al., 2014), but such relations seemed strikingly absent among our participants." This suggests that effective communication for the MoBE may differ in important ways from communicating other microbiomes.

Besides doing good as individuals, authors also wrote about doing good for the collective. For example, authors argued that the benefits of microbiome research needed to reach a wide range of people. This can be seen when Lange et al. (2022, p. 4) ask, "How do we ensure that future, potentially disruptive, microbiome knowledge-based, and microbiome-derived treatments in the health and food system and beyond are being developed globally, for the benefit of all, supporting environmental, dietary, and ethnic diversity?" One solution to Lange et al.'s question is increase in representation as can been seen when Abdill et al. (2022, p. 8) writes "The field would benefit from a more global perspective on investigating the human microbiome's relationship to health and disease."

4.2.3 Autonomy (C)

Autonomy is defined by the recognition of individual rights and the importance of free will (Beauchamp & Childress 2013; Mathews et al. 2022; Trump et al. 2023). 64 of our 83 articles referred to autonomy and authors discussed autonomy in the context of the right to do various things. These rights discussed below in more detail included the right to privacy, the right to either change or keep an individual's microbiome, and the right of microbiomes themselves.

Regarding privacy, authors commonly focused on how microbiome research could create another layer of surveillance or discovery of anonymized research participants. For surveillance, Clarke et al. (2017, p. 144) wrote, "However, as the taxa composition in a microbiome can also reveal details of a person's lifestyle and health, including those not germane to any legal issue, maintaining a similar database for microbiome data would inherently raise privacy issues not shown by DNA fingerprint databases." Here the concern is that microbiome data that is used for forensics could create another form of surveillance by states against people like current issues with the storage of genetic information. In the context of research, authors are instead worried about the possibility of identifying research participants through their microbiome data. This can be seen when Cho (2021, p. 1) wrote about the use of human microbiome association studies (HMAS) to identify people, "I demonstrate that a simple test statistic based on the taxonomic profiles of an individual's microbiome along with summary statistics of HMAS data can reveal the membership of the individual's microbiome in an HMAS sample." As our understanding of the MoBE improves, it may become increasingly easier to track and uncover information about a person based on what microbes they leave behind on surfaces.

Control over a person's microbiome appeared when authors discussed either a person's right to change it or to not have it be changed by others. For example, Gimbert and Lapointe (2015) make the argument that people should be allowed to track and modify their microbiomes:

> Despite the controversy about non-medically trained people taking full responsibility of their own bodies and making behavioral changes to achieve personal goals, this will not stop [11]. This trend is here is to stay and unlikely to be reversed. Instead of rejecting it on scientific grounds, we should address it by developing standard protocols for the framing of participant-led research involving self-tracking. Instead of refusing it on ethical basis, we should think about novel ways of assessing informed consent, anonymity, and transparency. A growing number of concerned individuals are demanding for socially robust citizen science [45], and self-trackers are a political force at the forefront of this movement. (p. 3)

Ma et al. (2018, p. 405) in contrast provide the point that the manipulation of one person's microbiome has the potential to influence others microbiomes as well, "Manipulating individual's microbiome in the hope of achieving better health should not be merely viewed as a technical or medical problem, which also has ethical implications as the changes may affect the surrounding community or society." Together there is a balancing act between allowing people to modify their microbiomes while not affecting others that do not intend to change their microbiomes. This will be an even greater problem for the MoBE as it requires balancing changing an entire space versus the desires of each person that enters that space.

Lastly, the study of microbiomes has raised the question of autonomy for microbiomes themselves. As mentioned earlier in individual good/non-maleficence, some have argued that microbiomes should not be harmed and some authors have taken this a step further by exploring if microbiomes have rights. For example, Wienhues (2022, p. 10) wrote about the challenges microbiomes make for biocentrism, "At least three non-exhaustive challenges are posed by the existence of microorganisms for biocentric environmental ethics theorising. These were (1) the moral significance challenge (2) the self-defense predicament, and (3) undermining individualist biocentric intuitions."

4.2.4 Justice (D)

Justice is defined by ensuring a fair distribution of benefits and costs across all individuals affected (Beauchamp & Childress 2013; Mathews et al. 2022; Trump et al. 2023). 61 of our 83 articles referred to justice.

Justice in the microbiome appeared in a few different ways. The first was justice in regard to who benefits from microbiome research. Mangola et al. (2022) captures this idea clearly in their argument for proper benefits sharing and prevention of exploitation by biopiracy:

> Indigenous communities are often disadvantaged in the research arrangement; they do not necessarily benefit from the conducted research and may not be fairly compensated for the advances that their contributions have made. The disclosure of compensation is essential in the consenting process and may necessarily occur at different levels (community, group, family, individual, and so on) but must be comprehensive and transparent so as to be equitable for all potentiation of research and returned benefits. Transactional relationships should be carefully embedded within research study development and procedures. (p. 752)

The second form of justice was criticizing how socially defined groups without power were portrayed in microbiome research. For example, De Wolfe et al (2021, p. 3) wrote, "In studies of the microbiome of the built environment, spaces are racialized but analyzed without explicit mention of race or structural racism." Here researchers are criticized for not acknowledging the influence racism has on socially defined races. Lastly, justice was talked about with regards to microbiome disparities between majority and minority groups. Amato et al. (2021, p. 3) shows the connection between space and microbial inequalities when they wrote, "Increased time spent indoors and reduced exposure to outdoor environmental microbes is also believed to reduce GM diversity (72, 73), and low SES and minoritized populations generally have less access to safe, outdoor green space compared to higher SES groups (74)." The issue of justice around microbial inequalities is one SEI of the MoBE that did appear in multiple sources with authors pointing out microbial inequities between both classes and socially defined races.

4.2.5 Public understanding, acceptance, and decision-making (A, B, C, D)

An SEI was trying to manage how publics understood, accepted, and made decisions about the microbiome. Public understanding, acceptance, and decision-making were the most discussed theme in our articles with 46 of our 83 articles mentioning the theme. Among the four ethical principles (A) individual good/non-maleficence (B) collective good/beneficence, and (C) autonomy were found in all 46 articles, while (D) justice only appeared in 28 of 46 articles. In most instances, authors focused on one-way conversations flowing from researchers to publics with various subsets appearing. Chuong et al. (2017) and other articles discussed how to best explain the results of microbiome research to participants and some articles discussed the merits of sharing results or not when microbiome science is still in the early stages of development. Other authors discussed how publics' trust and acceptance of microbes could be increased such as when Dudo et al. (2018) explored which microbiologists communicated with publics and how microbiologists could do it better. A final subset of these articles focused on understanding how publics made decisions about the acceptance of microbes such as when DeSalle et al. (2022) and Zichello et al. (2021) tried to capture different publics' understanding of microbes as it related to human healthcare. Based on our sample for the MoBE there is a lack of knowledge about what publics think about the MoBE or what their non-attitudes are about this nascent area of research.

4.2.6 Policy and regulation (B, D, A, C)

The SEI here was deciding what should be regulated/policies made and how should the benefits and costs of regulations/policies be distributed. Policy and regulation of the microbiome appeared in 24 of our 83 articles. Among the four ethical principles (A) individual good/non-maleficence appeared in 22 of 24 articles (B) collective good/beneficence was in all 24 articles (C) autonomy appeared in 21 of 24 articles, and (D) justice was in all 24 articles. Articles could be separated into discussions about either regulating the use of microbiome technology development or policies for how microbiome science could be implemented through policy and regulation. Difficulties surrounding regulating the microbiome were best captured in Darling et al. (2015) title "what is the FDA Going to think?…." Here and in other articles, authors discussed the difficulty of knowing where microbiome applications currently fit into the regulatory landscape. In policy making, related to privacy concerns, Clarke et al. (2017) discussed the potential use for microbiome science in forensic investigations, but pointed out the need for policy about when microbial data can be admissible in court.

It was not discussed in our sample, but in the U.S.A., microbial products that are genetically engineered would be regulated under the Coordinated Framework (EPA et al., n.d.). The USDA would be responsible for microbes that are plant pests under the Plant Protection Act (Wozniak et al. 2012). The FDA would be responsible for microbes that fall under the Federal Food, Drug, and Cosmetic Act used for food or feed. Lastly, the EPA would be responsible for the regulation of microbes that fall under either the Federal Insecticide Fungicide and Rodenticide Act (FIFRA) (act as biopesticides or the Toxic Substances Control Act (TSCA) (for genetically engineered microbes that are intergeneric—engineered with genes coming from different species) (Wozniak et al 2012). Among these agencies, which agencies will regulate a specific product for the MoBE will depend upon both what process was used to create a product as well as the purpose of the product (e.g., whether engineered to reduce pests under FIFRA or for general use and release into the environment under TSCA) (Wozniak et al. 2012). Because genetically engineered microbes for indoor use are not likely to be plant pests or used for food and feed, EPA is the most likely regulatory agency with authority under TSCA or FIFRA.

4.2.7 Representation in research (B, D, A, C)

The SEI with representation in research is ensuring that a diverse set of people across socially defined groups take part in research. Representation in research was in 18 of our 83 articles. Among the four ethical principles (A) individual good/non-maleficence appeared in 16 of 18 articles (B) collective good/beneficence was in all 18 articles (C) autonomy appeared in 11 of 18 articles, and (D) justice was in all 18 articles. Most articles focused on who the research participants were. Abdill et al. (2022), for example, makes representation explicit in their title: "public human microbiome data are dominated by highly developed countries." Commonly, these authors pointed out that current data about humans in the microbiome usually only included large amounts of data on white people from affluent areas of their country. Or worse, authors like Fortenberry (2013, p. 165) point out a lack of data on different socially defined groups when he writes "however, in many microbiome-related studies, race/ethnicity is not mentioned at all." Allali et al. (2021) is one of the few exceptions that focus on representation both in who is being researched and in who the researchers are. For example, Allali et al. (2021) write:

> The countries where most studies were conducted were in East and Southern Africa. This may be influenced by the fact that most of the first and last authors who had multiple affiliations (from both African and non-African institutions) were from East and Southern

> Africa. Therefore, these scientists have more opportunities through their North American/European affiliations to foster collaborations outside Africa and also secure funding for microbiome studies in these specific regions of the continent. Another reason for the over-representation of Eastern and Southern Africans in the microbiome studies may be the higher prevalence of HIV in these parts of Africa (20 million in Eastern and Southern Africa compared to 6 million in West, Central, and North Africa collectively in 2018 [43]. As a high proportion of studies focused on HIV/AIDS (29/168 compared to less than 10 for any other disease), it follows that more of such studies will be situated in these two regions to permit the recruitment of required large numbers.
> However, Africans have widely different genetic and cultural backgrounds [16] and this diversity may affect their microbiomes [1, 35, 44]. This variability argues for broader coverage of residents of Africa from all regions in microbiome studies. (p. 46)

Showcasing both who in Africa can conduct microbiome studies and subsequently who gets studied as well. The MoBE just like other microbiome research could end up with a similar issue of focusing on only BE of areas easily accessible to western researchers unless an effort is made to increase diversity of people studied in the MoBE.

4.2.8 Decolonizing microbes (B, C, D, A)

One of the SEI prominent in the articles was the need to address issues associated with neocolonialism in thinking about microbiome engineering. Decolonizing microbes was in 18 of our 83 articles. Among the four ethical principles (A) individual good/non-maleficence appeared in 10 of 18 articles while (B) collective good/beneficence (C) autonomy, and (D) justice were found in all 18 articles. In this theme authors focused on ways that colonialism affected a person's or environment's microbes and how these peoples or places can become decolonized. Precision microbiome engineering may also be seen as a form of neocolonialism if local communities are not engaged in decisions affecting how or whether their microbiome is manipulated. Many authors discussed how scientific practices related to studying and engineering microbiomes reflected the exploitative nature of colonialism. For example, Benezra (2020) writes.

> Conceptually, microbiome science is race free, but subjects of microbiome research are often placed in familiar, opposing groups: "Westerners"[9] who are primarily white and are assumed to have similar lifestyles and socioeconomic statuses, versus black and brown bodies in the global south assumed to be underdeveloped or "modernizing" (p. 882)

This theme of white bodies versus black and brown bodies appears in others works as well like Greenhough et al. (2018) where being white is associated with being clean while being black is associated with being dirty. Besides this criticism, authors made various arguments for how microbes could be decolonized such as Abdill et al. (2022) calling for the benefits of microbiome research being shared with the indigenous peoples studied or Warbrick et al. (2023) who discussed the inclusion of "indigenous perspectives" in the research of microbiomes. For the MoBE acknowledgment of indigenous places and displacement from them will play an important role in decolonizing the MoBE.

4.2.9 Ownership and privacy (A, C, B, D)

The SEI here is concerns over who owns what and who can maintain their privacy in the context of the microbiome. Ownership and privacy was in 18 of our 83 articles. Among the four ethical principles (A) individual good/non-maleficence appeared in all 18 articles (B) collective good/beneficence was in 15 of 18 articles (C) autonomy appeared in all 18 articles, and (D) justice was in 15 of 18 articles. In terms of ownership, Hawkins and O'Doherty's (2011) title captures it well when they ask, "who owns your poop?". Similar, but different to genetic concerns over who owns and subsequently benefits from genetic data, there are unresolved concerns over whether the microbes that a person has acquired still belong to them, especially when associated with waste like poop. In terms of privacy, this concern showed up in two different ways. The first was that authors like Rhodes (2016) write.

> Approximately, 95 % of my feces are microbiome, and my microbiome tells the story of where I have been and with whom I have associated. Should law enforcement agents have access to my microbiome in the same way that they are allowed to collect my fingerprint trail? (p. 2)

In these instances, privacy is concerned with the ability to track people or uncover information about them that they want to keep private. The second is when authors like Franzosa et al. (2015) write about their ability to identify people based on different microbial data points. This raises concerns for research participants being reidentified after public databases are released even if any human contamination has been excluded. Interestingly though, respondents themselves in McGuire et al. (2012, p. 10), appeared relatively unworried about privacy risks as the authors wrote, "recruits were largely comfortable with data sharing in the HMP and saw few privacy related risks posed by having their data shared." Researchers studying both participants and the MoBE might uncover information that participants would have wanted to keep private. Researchers will need to consider in advance what they would do if they found such information.

4.2.10 Microbiomania (A, B, C, D)

"Microbiomania" are instances of obsession with the potential for microbiome science to revolutionize society in some way. Microbiomania was in 16 of our 83 articles. Among the four ethical principles (A) individual good/non-maleficence and (B) collective good/beneficence appeared in all 16 articles (C) autonomy was in 14 of 16 articles, and (D) justice was in 13 of 16 articles. These articles commonly criticized the hype of microbiomes with titles like Ma et al.'s (2018) "Help, hope and hype…" or when Nieves Delgado and Baedke (2021) write.

> Based on these empirical problems, biologists and philosophers of science have cast doubt on the strong causal role of the microbiome in human health and development. Especially in cases of obesity and mental health explanations, microbiome causality merely shows low stability and specificity (Lynch et al., 2019). Thus, against catchy slogans like 'you are what you eat' (Zmora et al., 2019, p. 25), which might stir hopes for personalized or group-specific health interventions, we should rather question whether recent human microbiome discoveries really have far reaching effects on our understanding of our biological identity, our 'self,' and what it means to be human (Parke et al., 2018, p. 4)

Like this criticism of the hype, other authors criticized how capitalism and market forces direct the development of microbiome science and applications. Ironstone (2019) captures this well in her discussion of TED talks about the microbiome where presenters whether for or non-profits attempt to construct their audience as potential investors into a new idea that will revolutionize the market. With the MoBE being the next nascent area for precision microbiome engineering we could expect hype and hope to appear in products proposed to create ideally BE to address various people's health concerns without ensuring that such results are possible.

4.2.11 Race and gender (A, D, B, C)

The SEI of socially defined race and gender in the microbiome is the improper use of these socially defined groups to study differences between them. Race and gender were in 16 of our 83 articles. Among the four ethical principles (A) individual good/non-maleficence appeared in all 16 articles (B) collective good/beneficence was in 13 of 16 articles (C) autonomy appeared in 9 of 16 articles, and (D) justice was in all 16 articles. In some of these articles, the term "Ghost variables" was used to describe instances where variables like "western" are used as proxies for socially constructed variables like "race" and these ghost variables treat race or other socially constructed variables as biologically innate (De Wolfe et al. 2021). The term "ghost variable" itself was not always used, but the concept was seen in other works such as Amato et al (2021, p.3) writing, "Furthermore, race and ethnicity/ancestry are often incorrectly used interchangeably." In most of these articles, ghost variables were described as instances where microbiome research reflected racist or colonialist views. Less common was the discussion of how sex could be used as a ghost variable. While the issue of studying gender was mentioned a few times in passing, Mulak et al. (2022) and Kim (2022) engaged in a more focused discussion on the use of terms like "microsexome" and "microgenderome" and criticizing the use of terms like "sex" by researchers when they appeared to either be studying gender or mixing aspects of sex and gender together with no distinction or forethought. Outside of our sample the recent NASEM Report (2023) "Using Population Descriptors in Genetics and Genomics Research: A New Framework for an Evolving Field" captures the same issue happening in genetics research. Researchers using either genetic data like in this report or the microbiome data from our sample fail to grasp the underlying societal factors that drive differences between socially defined groups. Like the solutions proposed in the 2023 NASEM report, research about the MoBE will need to have very careful guidelines about when and how socially defined groups should be studied to not end up as ghost variables.

4.2.12 Stigma, discrimination, and bias (C, D, A, B)

The SEI here is stigma, discrimination, and bias being formed based on the microbes a person either has or others assume that person has. Stigma, discrimination, and bias were in 12 of our 83 articles. Among the four ethical principles (A) individual good/non-maleficence and (B) collective good/beneficence appeared in 10 of 12 articles, while (C) autonomy and (D) justice were in all 12 articles. In these articles, authors focused on how microbes might be used to discriminate against someone either for insurance or socially. Elhaik et al. (2021), for example, writes.

> Given all the identifiable information that is present in a sample and all the metadata about people that are being collected, a new risk of discrimination is now an issue. Unfortunately, legal frameworks, like GINA [6] and equivalent US state statutes, do not prevent life insurance underwriters from changing their premiums based on genetic markers—even if the markers were taken from genetic material left on a drinking cup (Fig. 1) or the saliva under the stamp or envelope that

> was mailed to the insurance company [68]. Moreover, any information about family members could also legally be used as a basis for altered eligibility, coverage, or premiums on life, disability, or long-term care insurance. By extension, any of the forensics mechanisms described above could potentially be used to change, deny, or alter coverage for a person or their relatives. These legal frameworks, designed to safeguard worker's DNA and genetic information, are frozen by the definitions provided by the legislature and thus do not apply to the epigenome, microbiome, or metagenome information. (p. 5)

This quote shows that while there are protections against discrimination based on a person's genes, it is unlikely that such protections would be extended to a person's microbiome. Social discrimination based on a person's microbes appeared in two different ways in the literature. First, authors like Fan et al. (2022) focused on testing if microbial aversion to visible negative health effects like diseased looking skin could explain intergroup bias with current research based on the articles examined being inconclusive. Secondly, Tanous and Eghbariah (2022) examined how microbes were over time intentionally associated with a socially discriminated group. In their case, they found that Palestinians in Israel became associated with brucellosis because Palestinian goat farmers were pushed away from Israeli efforts to vaccinate or cull livestock against the disease. For the MoBE discrimination, stigma and bias may appear through certain areas being associated with "bad" microbes and subsequently anyone from that area being lesser than because they live in a "bad" BE.

4.2.13 Microbes reflect inequalities (A, B, C, D):

The SEI for this subsection is that microbial differences are connected to inequalities between socially defined groups. Microbes reflect inequalities was in 10 of our 83 articles. Among the four ethical principles (A) individual good/non-maleficence (B) collective good/beneficence (C) autonomy, and (D) justice appeared in all 10 articles. In these articles, different authors highlighted various ways inequalities could happen in the MoBE and provided suggestions for what could be done to address these inequities. Ishaq et al. (2019, p. 5) writes about the distribution of green spaces and their connection to microbial inequalities, "The distribution of these amenities themselves has implications for equity (i.e., spatial justice), because such facilities often accompany redevelopment projects or new development rather than older neighborhoods." Subsequently, the authors argue for equitable-based zoning that improves the state of older neighborhoods to encourage greener spaces and reduction in pollution. Choudoir and Eggleston (2022) echo these sentiments when they write.

> Increasingly, we understand that disrupting environmental microbiomes amplifies social inequities, reinforces disproportionate access to natural resources, and perpetuates historical legacies of injustice. Across the urban to rural continuum, communities that rely on the local environment, due to cultural connection or necessity, are more susceptible to environmental harm (27–29). Green space (e.g., park, garden, arboretum) proximity and accessibility across global urban areas correlates with socioeconomic status, income, age, and education but inversely correlates with pollution exposure (30–32). Important health benefits associated with access to green spaces include improved mental and physical health and long-term reduction in mortality (32–34). Environmental microbiome exposures in green spaces relate to similar health benefits (35–37) and conversely, the biodiversity hypothesis suggests that reduction of environmental microbial exposures negatively impacts human health (38). (pp. 2)

To restore these microbial communities, others like Ironstone (2019, p. 335) call for "affirmative microbiopolitics" where the norm becomes a restoration of a person's microbiomes to a healthy state. Ishaq et al. (2019, 2021) and Robinson et al. (2022) take the lead though for discussions of inequities in microbiomes and their restoration as these sets of authors have formed a working group called "Microbes and Social Equity Working Group" which encourages research and discussions around the intersections of microbiomes and social equity. Researchers working in the MoBE will benefit from being mindful of and building upon the work of the Microbes and Social Equity Working Group to explore how microbial inequalities are perpetuated and can be addressed in the MoBE.

4.2.14 The rights of microbes (A, C, D, B)

The SEI is deciding on what rights if any microbes or microbiomes have. The rights of microbes was in 7 of our 83 articles. Among the four ethical principles (A) individual good/non-maleficence appeared in all 7 articles (B) collective good/beneficence was in 4 of 7 articles (C) autonomy, and (D) justice appeared in all 7 articles. For this theme, most articles engaged in philosophical discussions of whether and when microbes had an innate right to exist outside of their utility to humans or other living organisms. Cockell (2005, 2011), Nolt (2017), and Wienhues (2022) engaged in such discussion focusing on the rights of groups of microbes to exist innately and how this disrupts or reinforces an individualist, biocentric view of environmental ethics. Greenhough et al. (2018, p. 10) in their citizen science experiment questioned if publics would care for the innate rights of microbes but found instead little care from their participants, "such tolerance, bordering on indifference, suggests there are limits to the willingness of our participants to care both for and about the domestic microbiome" suggesting that at least some members of different publics do not care for the rights of microbes. Lastly, Bapteste et al. (2021) provides a section that discusses the possibility for microbes to hold legal rights like those held by other non-living entities. For the MoBE, it is currently unlikely that participants will have much ethical consideration for the rights of microbes being changed, but legal rights may appear if an environmental ethics argument can be made for the rights of a microbiome to exist independently of human interests.

4.2.15 Human health benefits and risks (A, B, D, C)

The SEI of human health benefits and risks is deciding who should benefit and how much from microbes and who should take the risks and how much from microbes. Human health benefits and risks was in 5 of our 83 articles. Among the four ethical principles (A) individual good/non-maleficence and (B) collective good/beneficence appeared in all 5 articles (C) autonomy was in 4 of 5 articles, and (D) justice appeared in all 5 articles. These articles discussed human health benefits and risks in one of two ways. First, Ma et al. (2018) and other authors brought up concerns over the unintended consequences of changing a person's microbiome. This is evident when O'Doherty et al. (2016) highlight the potential for one negative health condition to be replaced with another negative health condition:

> For example, although destroying harmful strains of H. pylori may seem to be beneficial in terms of decreasing stomach cancers, by destroying such bacteria too early we may inadvertently increase the chance of developing asthma or allergies early in life. (p. 417)

Second, Chuong et al. (2017) brought up the potential to change another person's microbiome unintentionally while treating a different person's microbiome. In this case, the impact of unintended consequences may go beyond the initial person being treated through their microbiome.

4.2.16 Need for social science (A, B, D, C)

The SEI for this subsection was a lack of inclusion of the social sciences in microbiome research. Need for social science was in 4 of our 83 articles. Among the four ethical principles (A) individual good/non-maleficence and (B) collective good/beneficence appeared in all 4 articles (C) autonomy was in 3 of 4 articles, and (D) justice appeared in all 4 articles. In these articles, authors made explicit claims that called for a greater inclusion of the social sciences in microbiome research. Two sets of authors emerged that discussed this theme in their work. The first is Benezra (2016, 2020) and Benezra et al. (2012) which mentioned or focused on how anthropology can improve microbiome science:

> Integrating anthropology into the design and interpretation of microbiome studies has the potential to take several forms: (i) to ethnographically investigate the impact of enrollment in microbiome studies on participants (how microbial terms and concepts are introduced; how these concepts are taken up in local, cultural, religious, and political contexts; and how they affect fundamental conceptions of the individual, family, and community) (ii) to study the impact of human microbiome studies on the investigators themselves, and (iii) to understand the transformative dynamic evolving from cross-disciplinary work (between biologists studying the microbiome and engaging with anthropology, and anthropologists engaging with human microbial ecology). (Benezra et al. 2012, p. 6380)

The second is the Microbes and Social Equity working group seen in Ishaq et al., (2019, 2021) and Robinson et al. (2022) who stress the importance of social sciences to avoiding false claims such as when Ishaq et al. (2021) write.

> For example, previous work investigating microbial mechanisms of health disparities has focused on how environmental, structural, and racial politico-economic discrimination and other inequities influence microbiomes, instead of falsely assuming inherent biological differences between people of different races (38). Interventions that ignore social interactions or neglect the social determinants of health may fail to meet their goals (44, 45). (p. 4)

Research on the MoBE we argue will benefit from the creation of diverse teams featuring experts across the natural and social sciences such as that seen in the Microbes and Social Equity working group.

4.2.17 Invasive methods (A, B, C, D)

The SEI of invasive methods is deciding when researchers should and should not use invasive methods to study the human microbiome and what invasive means to different groups. Invasive methods was in 4 of our 83 articles. Among the four ethical principles (A) individual good/non-maleficence (B) collective good/beneficence (C) autonomy, and (D) justice appeared in all 4 articles. In these articles, some authors like Hawkins and O'Doherty (2011, p. 4) focused on how what "invasive" means could vary based on "individual subjective and cultural acceptability of the actual research." Meanwhile, others like McGuire et al. (2008) focused on invasiveness in terms of how involved collecting data on a person's microbes would be such as the comparison they made between vaginal swabs being non-invasive versus an endoscopy being invasive. In the context of the MoBE, invasiveness may change instead to mean how modifying the BE could incidentally change an occupant's microbiome without their consent. Hence, the alterations to the microbiome may "invade" an occupant's microbiome without them potentially knowing what it is happening. The idea of consenting to the possibility of having one's microbiome changed by entering a modified MoBE will need to be explored further.

4.2.18 Environmental benefits and risks (A, B, C, D)

Like the SEI of human health benefits and risks, environmental benefits and risks is about deciding who should benefit and how much from microbes and who should take the risks and how much from microbes. Environmental benefits and risks was in 3 of our 83 articles. Among the four ethical principles (A) individual good/non-maleficence (B) collective good/beneficence (C) autonomy, and (D) justice appeared in all 3 articles. Each of these articles dealt with the potential environmental benefits and risks in different areas with the MoBE commonly appearing. Greenhough et al. (2020, p. 5) in their development of social science questions for the microbiome focused on sustainability when they asked: "What are the implications of the microbiome for prevalent approaches to sustainability: welfare, localism, chemicals?" Slashinski et al. (2012) called for the study of environmental contamination that could come from the exponentially growing use of over-the-counter probiotics. Lastly, Robinson et al. (2022) engaged in a more thorough discussion of the environmental benefits and risks of microbiome sciences by exploring four different questions for the use of microbes in environmentally equitable ways. These questions focused on the effect pollution has on microbiomes, how climate change could impact microbiomes, how microbiome inequities appear in urban environments, and how researchers and policymakers can create and implement methods for promoting a safe and healthy environmental microbiome.

4.2.19 Public engagement (A, B, C, D)

The SEI here is public engagement where a two-way interaction happens between researchers and publics. Public engagement was in 2 of our 83 articles. Among the four ethical principles (A) individual good/non-maleficence (B) collective good/beneficence (C) autonomy, and (D) justice appeared in all 2 articles. These articles were Hodgetts et al. (2018) and Lorimer et al. (2019) which both reported on the same citizen science project where the focus was on making the study of the domestic microbiome available to the public. In these articles, the authors discussed their challenges and successes engaging with publics about studying the microbiome. In terms of challenges, Hodgetts et al. (2018) wrote.

> The project biologist increased the conceptual sophistication of his explanations as the participants gained more experience with the technologies and terminologies. This was not always a smooth process, but our project was not merely an attempt to educate our public as per the "deficit model"—in which scientists have a pre-established set of knowledge that they wish to impart to an audience—which is assumed to be homogenous and ignorant [9]. Instead, we were facilitating a form of apprenticeship in which the participants set the questions and direction of research. (p. 3)

Here, the authors tried their best to meet the participants where they were in terms of knowledge and enable them to learn more at their own pace and discretion. In terms of success, Lorimer et al. (2019) discuss how performing different experiments influenced participants' perceptions of microbes into a more nuanced conversation about the microbiome:

> Thinking hygiene with microbial ecologies in a group setting over time put some of our (sometimes trenchant) ideas about hygiene at risk and forced us as a group to think about cleaning differently. By the end of the process, participants agreed that being clean was not indexed to the absence of microbes but related more to the absence of visible dirt and/or noxious odors. They reported a broad tolerance for commensal bacteria – the ones that are there and do us no harm. This tolerance grew as their experiments revealed the limited effects of their cleaning interventions on the diversity and abundance of the kitchen microbiome and thus the impossibility of sterility and microbial eradication. (p. 536)

For the MoBE nuanced public engagement that is molded to meet the interests and understanding of the publics being engaged will be important to effective discussions between researchers and research participants.

5 Discussion

In this study, we critically reviewed the extant literature regarding SEI of microbiome engineering, and through our analysis, we identified several themes. To organize and categorize these themes, we employed a framework developed by the NASEM for governance of emerging technologies that at its highest level consists of four ethical principles: individual good/non-maleficence (A), collective good/beneficence (B), autonomy (C), and justice (D). At the secondary level, these four principles underlie governance policy and SEI issues that we categorized into 15 themes. By applying this framework, we aimed to understand the societal and ethical dimensions of each theme and determine which ethical principles were most relevant to them.

We found that most articles in our review did not reference the MoBE (71%) with a small subset of them referring to the MoBE in some manner and only one focusing exclusively on the MoBE (21%). The most common theme was "public understanding, acceptance, and decision-making" while "public engagement" was the least discussed. A small subset of our themes featured multiple articles that referred to the MoBE such as "microbes reflect inequalities," "decolonizing microbes," or "environmental health benefits and risks." This means there are multiple areas where the nuance of the MoBE has not been explored, such as "representation in research" or "public understanding, acceptance, and decision-making." 31 of our 83 articles made suggestions for addressing the SEI of our 15 themes which included the use of frameworks, like ethical, legal, and social implications (ELSI), treating socially defined groups as nuanced composites of different people, and the equitable treatment of research participants (Benezra 2020; Chellappoo & Baedke 2023; Tamburini et al. 2022).

Future research can build upon this work by exploring various ethical challenges, including difference between uses of the microbiome and different ethical lenses and philosophical perspectives that can inform and guide studies of the MoBE. In terms of applications, there are many potential interventions for microbiomes that could have different cascading effects, like engineering the microbiome of a person's skin, fecal transplants, changing the structure of a space (like adding plants), or directly altering a space's microbiome. In most cases, our ethical lens would help us consider the impacts on that individual, but what if it affects other people around that individual? If we start to consider others, then the ethical impact of a fecal transplant becomes much different if it only affects versus one individual versus an environmental intervention, like changing the microbiome of a shared space. A biomedical lens could come to a much different conclusion than an environmentalist or posthuman lens about who/what matters in an intervention. In most cases our articles focused on changing individual's microbiomes under a biomedical lens than changing an environment's microbiome under an environmental or other ethical lens. Furthermore, there is the need to consider others beyond people like the microbiomes of pets in the BE which were rarely if ever discussed. Considering the well-being of pets raises questions about how people should treat their pets' (or any others) microbiomes in addition to their own and their shared built environment. Lastly, there was a lack of introspection on what constitutes "health," the "environment," and what a "healthy MoBE" meant to the authors (Formosinho et al. 2022). The definition of each of these terms could impact people using the same ethical lens. For example, under an environmentalist perspective if a person defines the environment of the MoBE more narrowly than another, then they may not even consider certain environmental impacts in their decision-making.

Our findings demonstrate that microbiome research holds great potential for advancing public health and environmental sustainability, but it also presents a range of social and ethical considerations that must be addressed upstream of technology development to ensure responsible and equitable practices. This paper recognizes the multifaceted nature of these implications and emphasizes the critical importance of addressing them to maximize the benefits of microbiome research and minimize potential harms. For example, the human health benefits and risks of microbiome sciences must be carefully examined, discussed, and regulated with deference to a variety of ethical principles. While microbiome interventions hold promise for improving health, the unintended consequences of altering a person's microbiome need to be considered. This includes the possibility of replacing one negative health condition with another or unintentionally impacting individuals other than the one being treated. Understanding these risks is crucial for ethical decision-making and ensuring that interventions are developed responsibly. Another key finding of the SEI of microbiome research is the need to decolonize microbial studies. Our paper highlights how scientific practices related to studying microbiomes can reflect the exploitative nature of colonialism. Recognizing and rectifying these historical inequalities is essential to ensure that microbiome research does not perpetuate further injustices. Efforts should be made to include diverse populations and to consider the ownership and control of microbial data and resources, empowering communities rather than reinforcing existing power imbalances that may likely lead to inequitable distribution of risks and benefits of microbiome developments.

Furthermore, our analysis revealed that almost all the themes cut across multiple ethical principles. This suggests that the SEI of the microbiome cannot be, nor should they be, neatly compartmentalized into distinct categories within our ethical framework, but rather, these implications often involve complex and interconnected ethical considerations that encompass multiple dimensions. Some themes demonstrated a clear alignment with one principle, while others exhibited a more nuanced relationship with multiple principles. This highlights the intricate nature of the ethical landscape surrounding the microbiome and emphasizes the need for a comprehensive and holistic approach to addressing these implications. As this field continues to develop, this analysis may serve as the fundamental bedrock of the SEI of microbiome research and development. By employing our framework, we were able to identify the primary

Table Appendix 1 Initial 31 codes from analyzing literature on the societal and ethical implications of microbiome research

Code	Definition	Articles
Communicating microbes	Instances where authors talk about who communicates, the language used, and/or challenges associated with communicating microbial concepts to others	32
Human microbiomes versus human genomes	Comparisons between the science of the human microbiome and the human genome	12
Indigenous microbes	The relationship between indigenous ways of knowing and interpretations of the microbiome	2
Lack of social sciences in microbiome science	Instances where microbiome research is accused of ignoring social factors in the study of human microbiomes	5
Methods, questions, and suggestions for social science in microbiome science	Different methods, questions, or suggestions given by authors for including social science perspectives in microbiome research	37
Microbes and citizen science	Instances where authors talk about using citizen science in microbiome research	1
Microbes and autonomy	Discussions of a person's right to not have their microbes changed intentionally or accidentally by others, the ability of people to test and study themselves, or the ability of people to consent and have rights over the use of their microbial information	13
Microbes and benefits sharing	Cases where authors discussed how the benefits of microbiome research should be distributed	1
Microbes and biosocial	Cases where authors argued that microbiomes should be studied as a "biosocial" process where both biological and social forces together influence microbiomes	1
Microbes and capitalism	Critiques or comments about the influence of markets on the development of microbiome science	15
Microbes and colonialism	Discussions of how the study of microbes is extractive or exploitive of different peoples	17
Microbes and culture	Instances where a person's culture influences their perceptions of microbe related activities	3
Microbes and environment	Instances where microbes are discussed in terms of their relationship to the environment we live in	3
Microbes and gender	Relationship between how a person's gender influences their microbes	8
Microbes and hype	Discussions of how microbiome research is being overhyped	9
Microbes and inequalities	Connections between microbes and inequality between different socially defined groups	9
Microbes and invasive methods	Discussions of how microbiome research methods can be invasive	4
Microbes and justice	Connections between microbes and providing justice to different groups of people	3
Microbes and ownership	Discussions of who should own microbial information	9
Microbes and politics	Instances where microbes are used as political tools	2
Microbes and positionality	Examples of the different publics that differ based on their perceptions of microbes	25
Microbes and privacy	Discussions of maintaining a person's privacy when someone else has information on that person's microbiome	17
Microbes and public knowledge	Instances where the public's knowledge of microbes or change in knowledge is discussed	4
Microbes and race	Connected between a person's perceived socially defined race and their microbes	10
Microbes and risk	Discussions of the physical risk of modifying microbes	8
Microbes and sense of self	Philosophical discussions of how new knowledge about the human microbiome either does or does not challenge our understanding of ourself as a human being	17
Microbes and stigma	Instances where stigma against certain groups is associated with knowledge about their microbes	12
Microbes policy making	Examples of past policy making or calls for policy making that focus on microbes in some way	5
Microbial rights	Philosophical discussions of the rights of microbes themselves	6
Regulating microbes	Discussions of how microbes research, commercialization, or use should be regulated or overseen	21
Representation in microbiome science	Discussions of how different socially defined groups are or are not represented in microbiome research	17

Table Appendix 2 31 initial codes transformed into final 20 codes

Final code	Initial codes
Autonomy	Microbes and autonomy
Justice	Microbes and justice
Collective good/beneficence	Microbes and benefits sharing
Individual good/non-maleficence	
Public understanding, acceptance, and decision-making	Communicating microbes, human microbiomes versus human genomes, microbes and biosocial, microbes and capitalism, microbes and colonialism, microbes and gender, microbes and hype, microbes and ownership, microbes and politics, microbes and positionality, microbes and privacy, microbes and public knowledge, microbes and race, microbes and sense of self, microbes policy making, regulating microbes
Policy and regulation	Communicating microbes, human microbiomes versus human genomes, microbes and capitalism, microbes and colonialism, microbes and hype, microbes and ownership, microbes and politics, microbes and positionality, microbes and privacy, microbes and public knowledge, microbes and sense of self, microbes policy making, regulating microbes
Representation in research	Communicating microbes, human microbiomes versus human genomes, indigenous microbes, microbes and colonialism, microbes and culture, microbes and privacy, microbes and race, representation in microbiome science, regulating microbes
Decolonizing microbes	Communicating microbes, human microbiomes versus human genomes, indigenous microbes, microbes and capitalism, microbes and colonialism, microbes and gender, microbes and hype, microbes and politics, microbes and positionality, microbes and privacy, microbes and race, microbes and sense of self, microbes policy making,
Ownership and privacy	Communicating microbes, human microbiomes versus human genomes, microbes and capitalism, microbes and culture, microbes and hype, microbes and ownership, microbes and positionality, microbes and privacy, microbes and public knowledge, microbes and sense of self, regulating microbes
Microbiomania	Human microbiomes versus human genomes, microbes and capitalism, microbes and colonialism, microbes and hype, microbes and ownership, microbes and positionality, microbes and privacy, microbes and public knowledge, microbes and sense of self, regulating microbes
Race and gender	Microbes and colonialism, microbes and gender, microbes and hype, microbes and race, microbes and sense of self
Stigma, discrimination, and bias	Communicating microbes, human microbiomes versus human genomes, microbes and capitalism, microbes and colonialism, microbes and culture, microbes and privacy, microbes and race, microbes and stigma, regulating microbes
Microbes reflect inequalities	Microbes and capitalism, microbes and gender, microbes and inequalities, microbes and ownership, microbes and positionality, microbes and race, microbes and sense of self, microbes policy making, regulating microbes
The rights of microbes	Microbes and sense of self, microbial rights, regulating microbes
Human health benefits and risks	Microbes and capitalism, microbes and positionality, microbes and risk, microbes and sense of self
Need for social science	Microbes and colonialism, microbes and gender, microbes and race
Invasive methods	Microbes and culture, microbes and invasive methods
Environmental benefits and risks	Microbes and capitalism, microbes and environment, microbes and politics, microbes policy making
Public engagement	Communicating microbes, microbes and capitalism, microbes and hype, microbes and ownership, microbes and positionality, microbes and privacy
Methods, questions, and suggestions for social science in microbiome science	Communicating microbes, indigenous microbes, lack of social sciences in microbiome science, methods, questions, and suggestions for social science in microbiome science, microbes and citizen science, microbes and capitalism, microbes and colonialism, microbes and gender, microbes and politics, microbes and positionality, microbes and privacy, microbes and race, microbes and sense of self, microbes policy making, regulating microbes

ethical principles relevant to each theme, highlighting the complex and interconnected nature of these implications. Moving forward, it is crucial to recognize and navigate the intricate ethical considerations associated with the microbiome to ensure responsible and equitable advancements in this rapidly evolving field.

Appendix: Transformation of codes from textual analysis

Table Appendix 1 provides in alphabetical order a description of all the 31 codes originally identified by the authors from our sample of 83 articles. Following this table, Table Appendix 2 provides an overview of how these codes were transformed into the paper's final set of 20 codes.

Table Appendix 2 provides an overview of which of the initial codes fed into the final codes presented in this paper. In many cases, the content of each initial code was separated out between the most applicable final codes. "Individual good/non-maleficence" was the only final code that did not have any initial code before its creation. The final codes are listed in order of their appearance in this paper.

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Author contributions JK had the idea for the article. AH, CC, and JK identified initial literature and systematic search parameters. AH performed the systematic review, forward citation search, backward citation search, and initial coding of the qualitative data. AH, CC, and JK all reviewed initial coding and developed them into our final set of codes. AH prepared all figures. All authors wrote and reviewed the main manuscript text.

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Declarations

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