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Microbiome ownership for Indigenous peoples

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Several studies have reported increased microbial diversity, or distinct microbial community compositions, in the microbiomes of Indigenous peoples around the world. However, there is a widespread failure to include Indigenous cultures and perspectives in microbiome research programmes, and ethical issues pertaining to microbiome research involving Indigenous participants have not received enough attention. We discuss the benefits and risks arising from microbiome research involving Indigenous peoples and analyse microbiome ownership as an ethical concept in this context. We argue that microbiome ownership represents an opportunity for Indigenous peoples to steward and protect their resident microbial communities at every stage of research.

The human microbiome is defined as a community of microorganisms (microbiota) residing in or on the human body, together with their genetic material and environment[1]. Human microbiomes contribute to physiological functions, such as food digestion and vitamin synthesis, and affect human health through protection against infectious agents, immune system training and immunomodulation[2–6]. Many studies have identified links between human gut microbial communities and diverse health conditions, including inflammatory bowel diseases, diabetes, allergies and mental health conditions[7–12]. Oral and skin microbial communities have been linked to periodontal disease, dental caries, eczema and psoriasis[13–16]. Therefore, understanding the microbiome and its interactions with human health is an exciting avenue for research and for the development of microbiome-based therapies, such as pre- and probiotics, microbiota transplant or therapeutic microbiota modulation[17]. This potential is reflected in a high level of research and commercial investment in the microbiome: as of 2019, more than US$1.7 billion had been spent on human microbiome research and more than US$3 billion invested in gut-microbiome-related biotechnology ventures[18,19].

A key step towards translational microbiota research is understanding the complex factors that shape human microbial communities. Current evidence indicates that some gut microbial taxa have speciated alongside humans and other primate hosts, suggesting that these host and microbial species have evolved along intertwined and mutually beneficial trajectories centred on host physiology and niche ecology[20–22]. At the scale of an individual human lifetime, acquisition of microbial communities begins at birth[23] and is shaped by a variety of influences, including diet, medication, other lifestyle and environmental factors, and possibly host genetics[24–36]. Awareness of these multiple inputs operating on the microbiome has prompted research on human microbiota variation across different lifestyles, ancestries and environments, with the aim of better understanding the factors shaping the microbiome in health and disease and their underlying mechanistic relationships.

A growing number of studies have specifically set out to analyse the microbiomes of Indigenous peoples around the world. Indigeneity is a complex concept that encompasses diverse peoples, and the right

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of Indigenous peoples to define their own membership and identity is key. Rather than attempting to conclusively define 'Indigenous', the United Nations (UN) Permanent Forum on Indigenous Issues has identified a series of elements that are often true of (but not essential to) peoples who define themselves as Indigenous[37]. These elements include self-identification as Indigenous; historical continuity with pre-colonial and/or pre-settler societies; strong links to territories and surrounding natural resources; distinct social, economic or political systems, language, culture and beliefs; and resolve to maintain and reproduce ancestral environments and systems as distinctive peoples and communities[38]. Researchers expect that studies of Indigenous peoples' microbiomes will contribute to the general understanding of human microbiota variation and support the eventual development of medical benefits[39,40].

The process of translating our understanding of the microbiome's role in human development, health and disease into products or therapies raises important ethical questions and concerns. For example, the question of who can be said to own human-associated microbiomes, or products derived from them, has important implications for the distribution of any future economic, social and health benefits arising from human microbiome research[41–43].

The scientific interest in Indigenous peoples' microbiomes makes assessing the ethical risks of any such research particularly important. Many Indigenous groups have experienced historic and ongoing mistreatment or injustice in the name of scientific and health research, and this legacy must be specifically acknowledged and addressed. Furthermore, any discussion of ownership necessarily invokes concepts that are culturally specific. For example, while ownership and intellectual property form a central focus of this piece, the concept of 'ownership' originates in a framework that primarily reflects European values and fails to describe viewpoints of Indigenous peoples as stewards and caretakers, rather than owners, of microbial communities.

Simply transferring ethical principles and frameworks developed in a Western context will not necessarily be suitable or relevant in an Indigenous context. Instead, a more nuanced and culturally aware approach is needed.

This paper represents a focused discussion of microbiome ownership in an Indigenous context. We are a team of Indigenous and non-Indigenous researchers with backgrounds spanning microbiology, genetics, bioethics and anthropology, who are all engaged in microbiome sciences. We acknowledge that our experience and expertise have developed mostly in the context of primarily English-speaking settler–colonial societies in both the Southern and Northern hemispheres, including Australia, Aotearoa New Zealand and the United States, and may be less relevant outside of these contexts. This piece is presented together with a complementary Article that outlines broad, guiding principles for ethical microbiome research involving Indigenous peoples, based on a framework of relationality[44].

In this Perspective, we discuss microbiome ownership with a focus on Indigenous peoples, who have largely been ignored in such discussions despite being an important focal point of microbiome research.

Table 1 | Historical overview of hypotheses linking microbes to non-communicable diseases

Hypothesis	Description	Refs.
Hygiene hypothesis	Articulates a link between microorganisms and non-communicable diseases, and proposes that reduced microbial exposure in early childhood increases children's susceptibility to allergens	128
Old friends hypothesis	Proposes that reduced microbial exposure causes humans to lose specific beneficial microorganisms that protect against non-communicable diseases	132
Biodiversity hypothesis	Proposes that reduced contact between industrialized humans and biodiverse environments impacts the human skin microbiota and its capacity to modulate the immune system	129
Disappearing microbiota hypothesis	Proposes that environmental changes in industrialized societies (such as cleaner water and antibiotic use) have interfered with intergenerational transmission of 'ancestral microorganisms', leading to changes in disease risk	130,131
Microbiota insufficiency syndrome	Proposes that the loss of microbial taxa and functions due to industrialization has created an evolutionary 'mismatch' between the microbiota and human genome, leading to misregulation of the immune and other body systems	40

Indigenous microbiome research

Several studies have aimed to characterize the microbiota of Indigenous peoples, typically comparing non-Indigenous individuals living industrialized lifestyles in the United States or Europe with Indigenous individuals living hunter–gatherer, or small-scale agriculturalist, lifestyles in the Global South[45–51]. Collectively, these studies have reported higher gut microbiota diversity and unique microbial community compositions in Indigenous or 'traditional' populations compared with industrialized groups. In addition, some studies have reported specific changes in the gut microbiota that have been associated with lifestyle transitions from 'traditional' to 'industrialized' or 'Westernized'[52–55]. One study that compared gut microbiota among four groups — Cheyenne and Arapaho Native Americans living industrialized lifestyles in the United States, a non-Native industrialized US population and non-industrialized Matsés and Tunapuco (Indigenous South American) populations — found that the Cheyenne and Arapaho harboured microbial signatures distinct from those of the non-Native industrialized population, but overall resembled the microbial signatures of this group more closely than they did those of the non-industrialized Matsés and Tunapuco populations[56]. Although fewer studies have examined oral or skin microbiomes of Indigenous peoples, several that do have also reported differences between Indigenous and non-Indigenous participants[50,57–59]. The handful of oral microbiome studies that include Indigenous individuals in industrialized settings have also identified systematic differences in diversity and composition between these individuals and their industrialized non-Indigenous counterparts[60,61]. These reports collectively indicate that Indigenous peoples around the world harbour microbiome signatures distinct from those of industrialized Euro-American populations, who otherwise dominate microbiome studies[62].

Many of these studies have tied the diversity of microorganisms observed in Indigenous peoples to 'traditional' aspects of their lifestyles. Furthermore, some of these findings have been interpreted to support a hypothesis that humans in industrialized societies have a depleted microbiome that is associated with increases in the incidence of non-communicable diseases, particularly metabolic and immune-linked diseases. This line of reasoning draws on earlier hypotheses about the relationship between microbial or environmental exposures and non-communicable diseases (Table 1). With a growing number of studies linking industrialized lifestyles to lower microbiota diversity, high-profile commentaries and reviews by leading human microbiome researchers have posited that loss of microbiome diversity, or 'microbiota insufficiency syndrome', underlies the increased incidence of non-communicable diseases in the industrialized world[25,40,63–67]. By extension, 'restoration' or 'rewilding' of the industrialized human microbiota to a more diverse and 'healthier' state has been proposed as a medical solution to protect against non-communicable disease[65–69].

As a result, a narrative has emerged regarding the scientific and commercial value of microbial species, genes, functions and communities found inside and on Indigenous bodies. In this narrative, the microbiota of Indigenous or 'traditional' peoples is framed as immensely valuable, perhaps the key to reversing the worrying increases in chronic non-communicable disease in industrialized settings. For example, prominent human microbiome researchers have argued that scientists must 'capture and preserve' unique gut microorganisms harboured by 'traditional peoples in developing countries' (many of whom are Indigenous)[65,66]. In anticipation of future health applications, researchers have established a not-for-profit Microbiota Vault to support the collection and storage of human-associated microbial biodiversity, with a 2 year launch phase for the initiative beginning in 2021 (The Microbiota Vault; https://www.microbiotavault.org/).

The benefit of this approach can be questioned on both technical and ethical grounds. Although microbiota signatures plausibly linked to industrialization have been identified, much work remains to untangle causal relationships and the precise impacts of geography, body site, host ancestry, and cultural or lifestyle practices in shaping microbial patterns and any related health effects. In addition, evolutionary experts have questioned the theoretical and empirical basis for microbiota 'rewilding', arguing that there is insufficient evidence to suggest that shifting microbiota to a 'less industrialized' state can have beneficial health effects[69,70].

From an ethical perspective, we find it concerning that, amid the burgeoning interest in Indigenous microbiomes, there has been little mention of the agency, rights or interests of Indigenous peoples at the centre of this proposed microbiome solution to non-communicable diseases.

For microbiome research to have the best chance of meeting its potential to improve human health and well-being, we must consider and address the ethics of how microbiome research is carried out, and to whose benefit or detriment.

Risks, benefits and harms in microbiome research

The 'restoration and rewilding of microbiota diversity' narrative contains uncomfortable echoes of exploitation or, at the very least, of unequal benefit. A key concern in this context is biopiracy, which is defined as the appropriation and control by non-Indigenous actors – usually for financial gain – of knowledge or resources that exist under the care of an Indigenous community[71]. One well-known example is the San *Hoodia* case, wherein researchers and a pharmaceutical company patented and attempted to develop a commercial weight-loss drug based on a plant used by the San people as an appetite suppressant, without acknowledging the San's position as knowledge holders or their rights to share in the potential benefits of commercialization[72]. Another example is the smokebush case, in which a US government department sought to patent anti-HIV products derived from a native plant found in Western Australia, without seeking the consent of, or offering to share benefits with, Aboriginal people who used the plant as traditional medicine[73].

Notably, one of the Microbiota Vault's stated aims is to collect and store microbiota samples from 'globally diverse human populations', particularly 'traditional' groups with minimal exposure to industrialization, in pursuit of future global health benefits[66]. This framing of target populations is also reflected in calls to 're-seed' the industrialized microbiota with 'lost' microorganisms maintained by "remote present-day peoples of traditional societies"[65]. This goal is reminiscent of earlier so-called vampire projects, such as the Human Genome Diversity Project and the Genographic Project, which aimed to survey the global diversity of human DNA by targeting 'isolated human populations', including many Indigenous groups[74]. Both projects proved controversial and were widely opposed by Indigenous peoples and organizations concerned about biopiracy and other risks[75,76].

Given the parallels, it seems prudent to consider in depth how present-day microbiota research initiatives can avoid repeating the mistakes of the past.

Even when stakeholders are not motivated primarily by economic gains, approaching Indigenous peoples' microbiomes as a resource to be mined to benefit the health of primarily non-Indigenous groups supports an extractive logic that minimizes the autonomy, agency and sovereignty of Indigenous peoples. A little over a decade ago, it was articulated how scientists use lofty goals to make inappropriate claims on Indigenous DNA[77]:

> "Native American DNA has emerged as a new natural resource that Native peoples possess but that the modern subject—the self-identified European—has the desire and ability to develop into knowledge."

These claims on Indigenous DNA were specifically linked to earlier claims made on Indigenous anthropological artefacts; it seems to us that microbiomes could be added to this list of Indigenous resources claimed by scientists in the pursuit of useful knowledge or a presumed 'greater good'. Although we acknowledge that advocates for the value of 'traditional' microbiomes are likely motivated by a genuine desire to improve the health of people suffering from chronic non-communicable diseases, a problematic imbalance remains. This imbalance arises because the narrative often espoused in research primarily values Indigenous microbiomes for the benefit that they are presumed to be capable of bringing to non-Indigenous communities, which can easily descend into treating Indigenous peoples as a means to an end[78]. Therefore, any initiatives seeking to study Indigenous microbiota must be carefully scrutinized and measures taken to avoid risks of biopiracy and other exploitative or extractive practices.

Harms can also arise from definitions of Indigenous or 'traditional' peoples that are used by microbiome researchers. Recently, cautions have been raised about the use of poorly defined and poorly justified racial or lifestyle categories in human microbiome research[78]. In using such categories, terms that may have a social or anthropological basis, such as 'ethnicity', 'geography' or 'genetic ancestry', effectively become racially coded. Although these terms are likely chosen by researchers precisely with the intention of avoiding racial categories, they nevertheless become racialized in how they are used and subsequently embedded within the scientific literature. Using broad, unexamined terminology can have the effect of collapsing and ignoring economic, political and cultural factors, which leaves vague, racialized categories as the presumed explanatory variable for microbiome differences[78]. Aside from being concerning from a social perspective, this also limits our ability to identify the mechanisms that shape the microbiome and human health. A recent editorial in *Nature* has outlined similar guidelines criticizing the use of racial or ethnic categories in biological research more generally, and requested that authors whose research deals with such categories provide more detailed information and reasoning about how they are defined and used[79].

In addition, 'microbiota insufficiency' promotes a sense of urgency in capturing 'wild' or 'vanishing' microorganisms from Indigenous populations for microbial 'restoration' or 'rewilding' efforts, without due regard for the rights, wishes or benefit of such populations. Perhaps this is because the urgency of the perceived need is seen as overriding such ethical considerations. In analogy to salvage ethnography, which aims to record so-called disappearing cultures, this approach was termed 'salvage microbiomics'.

Instead of supporting Indigenous or 'traditional' communities to maintain the heritage and environments that likely sustain their diverse microbiota, why are researchers calling for microbiota to be dissociated from their human hosts and used for the benefit of others?

Overall, we think that insufficient attention has been paid to fundamental bioethical questions of informed consent, data ownership and governance, and benefit sharing. For example, why should Indigenous peoples participate in such projects? Who will own and control the data and products created through this research? How will the central role

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of Indigenous communities in microbiome research be recognized and bring direct economic and social benefit to Indigenous individuals and communities? And how will the risks to Indigenous communities be minimized or regulated? Very few publications currently address such questions or offer strategies to address potential ethical pitfalls — a situation made all the more concerning in the context of centuries of repeated scientific misconduct experienced by Indigenous communities.

However, microbiome ownership rights could provide a mechanism to protect Indigenous microbiomes from exploitation, and even enable Indigenous peoples to drive and benefit from commercially translatable research. At present, the nature and scope of such rights have not yet been explored in relation to the microbiome. Next, we discuss ownership and governance of research data in the Indigenous microbiome space.

Indigenous microbiome data sovereignty

Indigenous peoples around the world have expressed a strong political desire for control of data and biological samples originating from research involving their communities. Because of historical and ongoing negative experiences[75,76,80–89], many Indigenous people do not trust non-Indigenous researchers or governments to handle their data or samples appropriately[86,89–91]. Advancing Indigenous data sovereignty has been proposed as a solution to counter misuses of Indigenous data and samples. As articulated in the seminal *Indigenous Data Sovereignty: Toward an Agenda*, Indigenous peoples have "inherent and inalienable rights and interests [...] relating to the collection, ownership and application of data about their people, lifeways and territories"[92]. Data sovereignty is therefore linked to self-determination as peoples and, in some cases, sovereign nations: "Indigenous data sovereignty thus refers to the proper locus of authority over the management of data about indigenous peoples, their territories and ways of life"[92]. Articulations of data sovereignty reflect not only a right to control and manage, but also a responsibility to care for, Indigenous data.

Calls for data sovereignty reflect a desire both to protect Indigenous data from misuse and to ensure that benefits from the use of Indigenous samples and data flow back to Indigenous peoples[93,94]. These goals can be supported by appropriate data governance mechanisms, such as the CARE (collective benefit, authority to control, responsibility and ethics) principles[95]. Systems and mechanisms to support Indigenous data sovereignty will also vary according to the specific Indigenous people(s) concerned and the political and legislative systems in which they operate[92]. The potential for data sovereignty principles to minimize the risks of inappropriate uses of Indigenous data, cultural harms and exclusion of Indigenous peoples from research benefits has been strongly articulated by Indigenous scholars, particularly in relation to human genomics[86,89,91]. However, data sovereignty is not limited to human data; genomic research that "draws on knowledge of [Indigenous] land, species and waters"[89] should be subject to the same considerations. Recently, the application of an Indigenous data sovereignty lens to data from biological anthropology research has been argued for, which can interface with ancient microbiome research[96]. Despite this robust body of literature and discussion in closely related fields, there has been a notable lack of direct engagement with Indigenous data sovereignty in the context of microbiome research.

We argue that data sovereignty principles are applicable to, and should be integrated in, the microbiome field. Human microbiome data are intrinsically tied to the human body and hence can give attributable information about an individual and potentially their health, environment and other aspects of their lives[97]. Microbiome data also have value for the community to which that individual belongs, as they have the potential to provide information on others within the community based on shared residence, environmental and interpersonal contacts, and other aspects of lifestyle. Importantly, many Indigenous communities view microorganisms as other-than-human kin to which they are obligated to maintain the right relationships and prevent harm. For these reasons, Indigenous data sovereignty principles should be implemented in microbiome research that involves Indigenous participants or stakeholders, whether the research aims are basic or applied.

The potential for translational products and commercialization raises further specific issues that microbiome ownership rights could help to address.

Intellectual property and Indigenous resource protections

In this section, we explore the legal landscape relevant to framing Indigenous microbiome ownership claims, primarily in the context of research that is translational or has commercial potential. The notion of 'property' in the Anglo-American legal tradition has undergone several transformations through time[98]. The political and social realities of whose property rights are recognized and protected have also changed over time, shaped by class, gender and race[98]. Intellectual property (IP), or "the legal rights which result from intellectual activity in the industrial, scientific, literary and artistic fields", is a specific subfield of property and ownership that is now predominant in Western legal systems and in international bodies that produce and enforce the protection of IP rights, such as the World Intellectual Property Organization (WIPO)[99]. These dominant global IP protection systems aim to support the expression of creators' moral and economic rights, the expression of the public's rights to access creations and the promotion of creativity and fair trading leading to innovation and economic and social development[99]. Copyright, patents and trademarks are examples of typical instruments of these IP protection systems. An important principle in such systems is the need to balance protection of the rights of creators against broader benefit in the form of the 'commons' or 'public domain'.

These globally dominant IP systems are not necessarily fit for the purpose of protecting Indigenous peoples, knowledge and resources in a culturally appropriate manner. WIPO defines 'traditional knowledge' as "knowledge, know how, skills, innovations or practices [...] passed between generations [...] in a traditional context"[100]. Similar terms to describe the broad concept of knowledge and practices developed and passed on by Indigenous peoples over time include 'Indigenous knowledge', 'traditional ecological knowledge', 'cultural heritage' and 'Indigenous cultural and intellectual property (ICIP)'. This type of knowledge challenges the dominant IP systems, which emphasize novelty, an inventive step and a clearly identifiable creator as conditions for IP protection. Instead, Indigenous systems of managing and protecting traditional knowledge typically emphasize the relationality between prior practice and new discovery, such that the identification of a discrete inventive step occurs in the context of collective efforts over time and in the community, rather than at a specific moment by a single creative individual. As a result, dominant global IP systems offer little protection against the misappropriation and misuse of traditional knowledge, which is usually classified as falling in the public domain[100].

Recognizing this limitation, international bodies including the UN and WIPO have made some efforts towards recognizing and protecting Indigenous peoples' interests in traditional knowledge. Some examples of international legislative instruments presenting articulations of Indigenous rights and interests in knowledge and resources are summarized in Table 2. These instruments highlight the importance of equitable sharing of benefits arising from the use of biodiversity and genetic resources, which are defined for the purposes of the Convention on Biological Diversity and the Nagoya Protocol as "any material of plant, animal, microbial or other origin containing functional units of heredity [...] of actual or potential value"[101,102]. However, these bodies may also constrain Indigenous ownership claims. For example, the UN Convention on Biological Diversity generally places the locus of ownership for genetic and other biological resources at the level of the nation state, rather than with Indigenous communities, and the Nagoya Protocol emphasizes recognition of Indigenous ownership of

Table 2 | International legislature articulating Indigenous rights and interests in knowledge and resources

Legislature	Key points	Refs.
1992 UN Convention on Biological Diversity	Preamble recognises the "close and traditional dependence of many indigenous and local communities embodying traditional lifestyles on biological resources" and importance of equitable benefit-sharing from the uses of biological diversity.	102
2007 UNDRIP	Article 31 states that Indigenous peoples have IP rights over their "cultural heritage, traditional knowledge, and traditional cultural expressions", including "manifestations of their sciences, technologies and cultures, including human and genetic resources, seeds, medicines, knowledge of the properties of fauna and flora [...]"	114
2010 Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from Their Utilization to the Convention on Biological Diversity (Nagoya Protocol)	Article 3 states that the Protocol "shall apply to genetic resources within the scope of Article 15 of the Convention [on Biological Diversity] and to the benefits arising from the utilization of such resources [and] to traditional knowledge associated with genetic resources within the scope of the Convention and to the benefits arising from the utilization of such knowledge."	103

traditional knowledge associated with genetic resources rather than Indigenous ownership of genetic resources per se.

Moving to the national scale, several countries have now introduced legislation aiming to regulate and protect traditional knowledge or cultural heritage[103]. A study has offered an in-depth exploration of the concept of ICIP in the Australian context. ICIP is defined as "Indigenous Australians' rights to their heritage", in which 'heritage' is in turn defined as[104]:

> "[...] intangible and tangible aspects of the whole body of cultural practices, resources and knowledge systems that have been developed, nurtured and refined (and continue to be developed, nurtured and refined) by Indigenous people and passed on by Indigenous people as part of expressing their cultural identity."

In this study, it is highlighted that, although Indigenous Australians have expressed a clear desire to define, own, control and protect their ICIP, these rights are inadequately protected under contemporary legal and policy systems[104]. Notions of IP that underlie existing Australian legislation are not commensurate with Indigenous Australian traditions of managing ICIP, for example, presumptions of a creative individual and time limitations on IP protection are not appropriate for governing ICIP, which is often held collectively and in perpetuity in accordance with specific cultural mechanisms[104]. (The Australian federal government has recently launched a new National Cultural Policy that includes planned "stand-alone legislation to protect First Nations knowledge and cultural expressions"[105]. However, the final form of the legislation is not yet known, and it is expected to focus on the arts rather than genetic or biological knowledge and resources.) Despite increasing awareness and discussion in recent years of the need for protections for Indigenous knowledge and resources, this question has not yet been extensively considered in relation to the human microbiome.

Ambiguity exists in patent protections

Conventional pathways within contemporary dominant IP systems can likely accommodate the patenting and commercialization of human-associated microorganisms and microbial products. In Diamond versus Chakrabarty, the US Supreme Court upheld Chakrabarty's claim to patent a bacterium that he had genetically modified to confer additional functions[106]. This case established precedent that living things, including microorganisms, can be patentable IP if they have been substantially shaped or altered through human intervention. In Australia, naturally occurring genes are excluded from patentability, but microorganisms, microbial products and microbial processes are all considered patentable[107,108]. WIPO also considers that genetic resources cannot be patented because they are not creations of the human mind, but that inventions developed using genetic resources may be patentable. Therefore, whereas naturally occurring microbial genes or species may be excluded from patentability in some jurisdictions, it appears that patentable inventions, such as microbiome-based therapeutics, could be generated based on human microbiome samples or data.

What is less certain is whether benefits from such commercialization would accrue to those who provided the samples or data in the first place. In Moore versus Regents of the University of California, the Supreme Court of California rejected the concept of self-ownership of the human body or products derived from it[133]. In this case, Moore's doctor and a research collaborator patented a cell line derived from spleen tissue taken from Moore's body during cancer treatment. On discovering this, Moore alleged that his cells had been stolen, and Moore's legal team argued that Moore should have a right to a share of the profits from the cells' commercialization. However, the majority judgement held that Moore's consent to removal of his tissues during medical treatment nullified his ownership interests in subsequent patenting and commercialization of products derived from his tissue[109]. Although this principle was established in relation to host tissue and has not yet been legally tested in relation to the microbiome, it is easy to imagine a similar argument being successfully deployed against claims to ownership of microbiome samples or derivative products by the individual or community from whom the sample was taken, provided that accepted consent processes for the initial sample collection are followed.

Furthermore, it is becoming apparent that corporations are currently focused on creating IP from nature, including microorganisms, at an industrial scale. In 2018, 38 million records of genetic sequences associated with patents were accessed and a database was created of 12,998 such sequences associated with 862 marine species, the majority of which were microbial[110]. A single corporation had registered 47% of the associated patents, exceeding the combined share of 220 other companies (37%), and universities and their commercialization partners had registered 12% of the identified claims[110]. A recent search of Google Patents, a publicly available IP and patent database, shows that the number of patent claims filed per year containing the term 'microbiome' has clearly increased in the past three decades (Fig. 1). Of the 192,813 total results, approximately 3.5% were registered by a single private corporation (10x Genomics), followed by another corporation (Nestec) and the Harvard Corporation, each registering approximately 2% of the claims. Although approximate, these figures illustrate the high level of commercial interest in microbiome-related IP.

However, describing the likelihood or feasibility of patenting does not answer the question of whether such outcomes are ethically desirable. Early work on the ethical, legal and social implications of human microbiome research highlighted the need to develop norms surrounding microbiome ownership to serve principles of justice and equitable distribution of benefits, and noted that 'cultural identities' may influence research participants' sense of microbiome ownership and research acceptability[41]. Subsequent work reasoned that microbiome ownership and patenting are not in the best interests of either science or society, preferring a 'science commons' model in which the contribution of microbiome samples is understood as civic participation in a collective enterprise[42]. However, some arguments rel on a fundamental framing of living things as private property, which cannot

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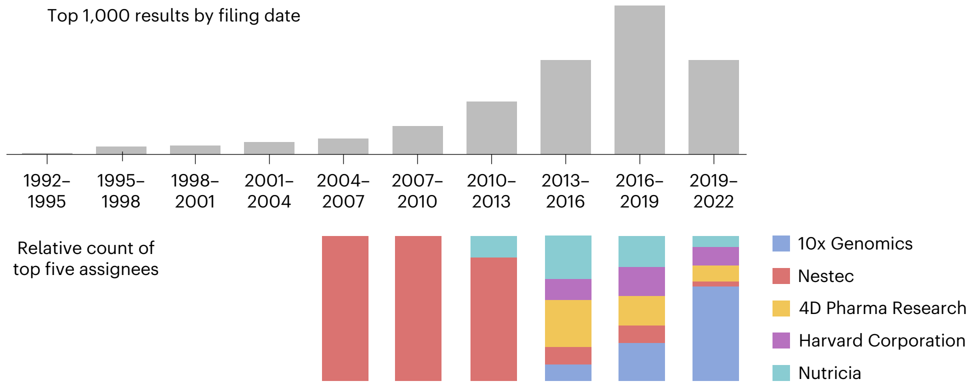

Fig. 1 | Summary of results from Google Patents search for the key term 'microbiome'. For the most recent 1,000 results, the number of records filed (grey bars) are presented in three-year blocks. Proportion of records associated with the top five patent assignees in each three-year period is indicated below the timeline by stacked coloured bars. Data are modified from Google Patents and current as of January 2022.

be assumed in all cultural contexts. For example, this view is directly contradicted by Goldtooth, executive director of the Indigenous Environmental Network: "Within most Indigenous beliefs, no person can own living things or hold life forms as property"[111]. Formulations of microbiome ownership ethics based on Western notions of property leave little room for communal ownership or cultural obligations to treat human-associated materials in a different way. Furthermore, appeals to the common good as a rationale for waiving ownership rights can be unconvincing when applied to communities who have been exploited and disadvantaged by such claims for generations. Regarding broad access to genomic data, it has been noted that[89]:

> "Critical reflection upon the notion of 'the public' presumes a notion of inclusion and representativeness that is often at odds with Indigenous experiences within colonial contexts."

In summary, international efforts towards protecting Indigenous knowledge challenge conventional approaches to ownership and IP surrounding biological materials and their derivatives. In the next section, we consider how this gulf can be bridged.

Protective frameworks for Indigenous microbiomes

Indigenous microbiome ownership could be conceptualized in several ways. Microbiome ownership rights could include straightforward property rights over physical microbiome samples and materials derived from them, such as microbial cultures. Indigenous peoples may also be able to claim rights under global dominant IP systems over data or inventions based on human-associated microorganisms, microbial communities or microbial products. A third angle to consider is whether human-associated microorganisms, microbial communities and microbial products fall under notions of traditional knowledge or ICIP and, if that is the case, what protection is available to them. These concepts and questions are not necessarily independent of one another. For instance, whereas patenting microorganisms and microbial products and processes is generally considered acceptable under dominant IP regimes, patenting and commercialization of microbiomes from Indigenous peoples may be restricted by international legal instruments such as UN Declaration on the Rights of Indigenous Peoples (UNDRIP), the Convention on Biological Diversity and the Nagoya Protocol. However, (legal) protection of microbiome data and samples under this framework likely hinges on whether human-associated microorganisms constitute a form of 'cultural heritage, traditional knowledge or traditional cultural expressions'[112] or are indeed a genetic resource[101,102]— questions to which there are currently no universally agreed-upon answers.

Indigenous scholars and international instruments for protecting Indigenous knowledge offer some guidance for charting answers to these questions. We recall that cultural heritage had been defined as[104]:

> "cultural practices, resources and knowledge systems [...] developed, nurtured and refined [...] by Indigenous people and passed on by Indigenous people as part of expressing their cultural identity."

Furthermore, Article 32 of UNDRIP states that[112]:

> "Indigenous peoples have the right to determine and develop priorities [...] for the development or use of their lands or territories and other resources."

Human-associated microorganisms could arguably be understood as a resource developed, nurtured and refined by Indigenous peoples and passed on over generations. This is the very logic underlying claims of state ownership over organisms whose development those countries have disproportionately contributed to, such as domesticated plants and animals that have been influenced by humans to meet their needs[101,113]. This principle of the mutual influence of human and natural worlds is common to Indigenous cultures that often do not see humans, non-humans and the natural world as separate entities, and also correlates with the social science concept of 'naturecultures'[114–117]. Only through the contextual interactions with people, place and other organisms could such microorganisms with potential therapeutic or beneficial properties arise. If we accept that traditional knowledge and practices have had a role in shaping living things, then the owners or custodians of such knowledge and practices may hold an ownership interest in these organisms. As human-associated microbial communities are influenced by host lifestyle, cultural factors and vertical transmission across generations, might not Indigenous peoples' traditional knowledge and cultural practices that have shaped their microbiomes be translatable into an ownership claim?

As tools are developed to increase the sensitivity and specificity of microbiome detection in ecosystems[118], there is a risk that further claims to IP, ownership and profits by actors external to Indigenous communities will only continue. Indigenous communities have typically not been included or invited to share in the benefits of IP-generating scientific processes. However, opportunities may exist for historically marginalized communities to create IP and, if desired, profit that could facilitate the development of circular economic systems to support community aspirations. This discussion cannot address the question of whether microbiome ownership or patenting is desired by Indigenous communities; communities will need to decide for themselves.

We argue that avenues to promote and protect Indigenous microbiome ownership should be explored. The recent growth in patent claims filed relating to the microbiome, and the dominance of large corporations and wealthy academic institutions among these claimants (Fig. 1), raises the stakes for protecting the rights of historically marginalized communities whose generations-long stewardship of microbial resources is currently going unrecognized. As the situation currently stands, ownership and IP rights likely have the potential to both help and harm. On one side of the coin, Indigenous peoples may wish to use global dominant IP systems to block claims of ownership and commercialization of their microbiomes by outside actors. On the other side, current dominant ethical and legal reasoning, which is rooted in Western cultural assumptions and demurs on ownership of genetic resources, may present a barrier to Indigenous claims to ownership and rights over the microbiome. The best way forwards may lie in new, culturally informed systems to recognize Indigenous rights and interests in microbiomes.

Outlook

Regardless of the exact forms and mechanisms of microbiome ownership that are eventually developed, the priority should be to respect Indigenous sovereignty and to support the right of Indigenous individuals and communities to lead these developments. Although questions of Indigenous engagement and sovereignty may be relatively new to many non-Indigenous researchers in the microbiome field, looking to guidelines for ethical conduct developed by Indigenous scholars and communities in related disciplines, such as human genomics and medical or pharmaceutical research, can provide a starting point[91,119–123]. Furthermore, ethical guidelines and recommendations specifically for microbiome research involving Indigenous communities are now being advanced[44,124,125]— for example, through the framework of relationality proposed in the accompanying Article[44]. Although our discussion here has focused primarily on microbial communities associated with human bodies, as these are currently the target of strong research interest, these framings may extend to microbial communities associated with, for example, soil or plants situated on Indigenous lands[126].

Microbiome researchers have an opportunity to avoid mistakes of the past and establish a positive legacy by adopting ethical frameworks that centre on Indigenous sovereignty.

There is a clear need in the human microbiome field to develop and implement strategies to support equitable sharing of benefits from research and commercialization with Indigenous participants and communities. Strong relationships and genuine partnership with communities will help to inform agreements about what benefits may be possible, desired and relevant to community priorities and aspirations. This process needs to begin with two-way discussions that identify potential benefits of research and how stakeholders will share them. This includes agreement on how any potential commercial applications will be handled for mutual benefit, before starting a research project. Agreements regarding both commercial and non-commercial benefit sharing may be formalized via a memorandum of understanding. Examples of non-commercial benefits include knowledge about the microbiome, eventual access to more effective microbiome-based treatments or therapeutics, or opportunities for training and infrastructure support. Options for sharing of financial benefits could include joint IP ownership and patent applications, discounts on downstream commercial products for community members whose samples and data aided the development of a medication or therapy[90], or rights to 'resale' royalties[104] in which community members are compensated for each subsequent commercial use of their data or samples. At a more systemic level, recent discussions have advanced suggestions for extending the Nagoya Protocol, which specifically focuses on equitable access and benefit sharing, to explicitly include digital sequence information, including metagenomic sequence data[127].

Building capacity and capability for communities to manage their own IP claims and potential commercialization is another mechanism for ensuring Indigenous peoples receive fair benefits from microbiome research. Currently, communities wishing to pursue IP claims may need to rely on assistance from non-Indigenous lawyers or university legal departments, which may not be ideal. Initiatives could include support for training and employment of Indigenous lawyers and patent clerks, or investment in institutions such as Indigenous-led IP think tanks, innovation accelerators and IP clearing houses. Existing Indigenous-led initiatives such as the Native BioData Consortium, IndigiData workshop and the international Summer Internship for Indigenous Peoples in Genomics (SING) programmes may be well placed to foster relationships, training and innovation to support Indigenous microbiome IP solutions.

Conclusion

Harnessing knowledge of the human microbiome holds great promise for improving human health and well-being. However, without equal attention to the ethical aspects of both fundamental and translational microbiome research, the field risks falling short of this promise. As Indigenous peoples have frequently been harmed by, or excluded from, the benefits of research, it is crucial to address how human microbiome research involving Indigenous peoples, either as participants or stakeholders, can be carried out ethically. We propose that microbiome ownership should be a fundamental concept in microbiome ethics that shapes how the benefits and risks of research are distributed, specifically in relation to Indigenous peoples. Engagement with the ethical questions we have raised, and the development of systems to support ethical research and benefit sharing, will be crucial as research interest in and the commercialization potential of the human microbiome continue to rapidly advance.

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Author contributions
M.H.-D. led the research and the drafting and revision of the paper. M.Z.A. contributed to the drafting of the paper and provided critical feedback and revisions. A.C.B. provided critical feedback and revisions. H.E.-T. visualized the data and provided critical feedback and revisions. K.F. contributed to the drafting of the paper and provided critical feedback and revisions. E.K. provided critical feedback and revisions. L.S.W. supported the conception and drafting of the paper and provided critical feedback and revisions. All authors approved the submission.

Competing interests
All authors, excluding H.E.-T., are currently or formerly involved in activities of the international SING Consortium, an initiative aiming to address the under-representation of Indigenous peoples in genomic research through workshops supporting Indigenous leadership and engagement in genomics. Specifically, E.K. is a current member of the SING Australia Organising Committee; M.H.-D. and L.S.W. are former members of this committee; M.Z.A. is a member of the organizing group for SING USA; A.C.B. and K.F. are current members of the SING USA faculty; and A.C.B. is a past SING workshop participant. M.Z.A. and K.F. are also members of the Board of the Native BioData Consortium, an Indigenous-led non-profit biobank and research institute based on the Cheyenne River Reservation in the United States. The Native BioData Consortium focuses on genomic research to benefit Native American health as well as Indigenous data sovereignty and educational initiatives, including the IndigiData workshop.

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