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Meanings, measurements, and musings on the significance of patterns in human microbiome variation

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Variation of the human microbiome is a multidimensional value depending on the question of interest. Unlike traditional human genetics, which most often deals with variation at the level of genes or genetic sequences, microbiome variation may be most relevant at the functional level and can be interrogated a number of ways. Most common methods are marker gene metataxonomic surveys or shotgun metagenomic sequencing, however more direct indicators of microbial activity that are gaining popularity include metabolomic and metatranscriptomic surveys. With all these data and promise in human microbiome research, it requires that we reassess what is meant by variation of the human microbiome and how its significance impacts the ability of microbiome research to be informative on a range of topics from evolutionary theory to clinical outcomes. Learning from mistakes is essential to advancing the field, and new sophisticated analysis tools are helping to crystallize associations between microbiome variation and its drivers so that firm ground supports future explorations of mechanism. However, the body of current data suggests that these may be highly individualized due to the array of interactions between the host, the microbiome, and the environment. As a result, microbiome researchers need to be cognizant of population contexts and the limits these impose on conclusive outcomes.

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Introduction

Variation of the human microbiome is different but related to variation in human genetics. For one, it is not vertically transmitted in a manner that faithfully depicts lines of ancestry, and two, its evolution involves environmental genetic contributions. One of the key strategies of the Human Microbiome Project (HMP) was to 'understand the range of human genetic and physiological diversity,' [1] by interrogating the microbiota throughout the human body. Therefore, 'range [. . .] of diversity' refers to intra-individual and inter-individual biodiversity that establish dimensional boundaries for interpreting the vast prokaryote genetic repertoire [2,3]. The genomes of cohabitating microorganisms are considered an accessory genetic landscape that are subject to selective pressures experienced or imposed by the host. Thus the human phenotype is the expression of trillions of genomes, dissolving notions of a singular self and earning the title of 'holobiont' [4]. The newly coalesced field of microbiome research encourages multi-omics data generation to relate microbial community composition and activity to host physiology.

Microbial activities entail neuroendocrine cross-talk [5], nutritional provisioning [6], changes to host gene expression [7–9], and immune training [10]. Some activities actually underlie developmental processes that impact host fitness, with putative epigenetic effects [11•]. In the hologenome concept of evolution, the holobiont is the unit of selection rather than individual genomes [12]. Proponents of this view posit that the microbiome facilitates macroevolution by affecting host behavioral, ecological, and physiological phenotypes [12]. I propose an alternative perspective that, as a result of accelerated adaptive response, the microbiome facilitates stabilizing selection on the host genome by nullifying extreme variants and maintaining reproductive viability in lineages that are ecologically diversified, such as humans. This is because the microbiome can rapidly acquire new functions through mutations or horizontal gene transfer [13,14].

The microbiome has certainly impacted human evolution [15], and group-level variation in taxonomic and functional features is well established [16–21]. However, variability also occurs at the individual level from ontogenetic interactions. Appropriate interpretations about causal interactions requires robust contextual metadata and interdisciplinary efforts among microbiologists, bioinformaticians, ecologists, clinicians, chemists, biologists, and anthropologists [22]. Since a thorough review on variation on the human microbiome was recently published [23],[1] my purpose is not to provide another exhaustive summary of the literature, but

[1] However I caution readers in accepting position points from any paper that makes coarse assumptions about subsistence transition states in human evolution and microbiomes, and discourage applying language such as 'ancient', 'primitive', or 'ancestral' to any modern living human population, and emphasize that 'modern' is not synonymous with urban–industrial societies, nor to any other one particular society or culture.

rather to synthesize studies that have improved the way we understand variation of host-associated microbiota, and chart a course forward. Along the way, an evaluation of paradigms, pitfalls, and strategies for improvement will be discussed.

What is microbiome variation?

Microbiome variation is multimodal and involves the entire ecological unit (the 'biome'), including molecules, genes, genomes, organisms, metabolism, and the environmental matrix [24]. Therefore, 'variation' can refer to taxonomy, phylogeny, gene category, gene copy number, gene expression, metabolic function, or the combined contributions thereof on host physiology. Additionally, variation can be quantified within or between individual hosts, since body sites and fluids harboring microbial populations evince compositional differences [25–29]. Variation will have different operatives depending on the objectives of the study and should be specified *a priori*. For example, gut microbiome variation in the context of population genetic history would look at strain-level variation, whereas dietary adaptations refer to *functions*.

Uncertainty remains about how the microbiome impacts human physiology, what factors may alter evolutionary fitness, and what traits may be heritable [30,31,32••,33–36,37••]. Simply finding an operational unit level relevant for differentiating human groups is a challenge. Often the operational unit is taxonomic and the hypothesis considers the presence or abundance of taxonomic units as adaptive host traits. However, associations between taxonomy and host phenotypes are tenuous, and taxonomic characterization of variation has resulted in conflicting findings, such as whether dominant taxa correspond to metabolic disease [38,39], or whether consistent disease associated microbiome markers even exist [40•]. Recent efforts to derive exact sequence variants from gene marker amplicon data [41–44] reflects a growing discontent with the standard practice of identity-based sequence binning [45] that may obscure informative but rare sequence variants. Increasingly the operative unit has expanded to include other structural (metagenomic), functional (transcriptomic, metabolomic, proteomic), and even codependent (guilds) elements [32••,46•]. Significant distinguishing features of microbiomes are likely based on ecological niche participation, and so data must capture information about microbial activity.

Another challenge is accounting for known variation to elucidate causal patterns. Public data are available for more than 40 human societies around the world, many of which are indigenous or rural cultural and ethnic groups (see Table 1). Yet few studies have made sufficient use of these data. Consequently, conclusions that would otherwise advance mechanistic models of host–microbiome phenomena are often not valid. The reluctance may stem from data compatibility issues due to a lack of standardization in data generation [47], but methodological advances alongside idiosyncratic study conditions eludes a universal protocol. Therefore, meticulous documentation of metadata, reagents, and procedures (including archival) should be provided unabridged with the final study report.

Regardless of methodological concerns, innovative studies are still hamstrung by not availing usable datasets that would lend greater confidence in the application of results. Accordingly, abundant literature demonstrates that subsistence economy, domestication, and captivity associate with dramatic restructuring of both human and nonhuman microbiomes [16,17,48–51]. Therefore, human and model-animal research needs to be cognizant of biases that may result from the exclusive use of westernized or market-integrated populations as well as non-wild or captive animals, especially of animal breeds that co-habitate with humans [52,53]. Furthermore, since nearly all human microbiome studies rely on associations with lifestyle traits, mode of subsistence for populations under study must be accurately characterized with an understanding of the historical and present-day social and political context [54,55]. To address these challenges, researchers should adopt methods that maximize data compatibility and identify limitations in the results. When traditional groups are studied or if research implications require a human evolutionary perspective, researchers should partner with group representatives and with anthropologists so that collaboration can lead to responsible research outcomes.

Broad patterns in microbiome variation across human populations

'Phylosymbiosis' of hosts and their microbiomes is a topical theme, which posits that as host genetic differences increase, so too will host-associated microbial community traits, due to the constraint of host ecologies [56•]. Such 'phylogenetic inertia' makes intuitive sense, and does not rely on both the host and microbiome undergoing vertically inherited transformations in parallel as implied in co-speciation or co-evolution. Furthermore, a phylosymbiotic model acknowledges and even predicts convergence of microbiome traits in response to shared host ecological niche, particularly diet [57–59]. Research on soil microbiomes demonstrates how comparable environmental factors induce community similarities, which patterns with ecological factors such as aridity, productivity, and pH, irrespective of geography [60•]. Thus, ecological participation best predicts microbiome assemblies. So far, the body of data on human microbiomes is consistent with this view, in that microbiomes of unrelated and remote-living human groups correspond on the basis of certain shared lifestyle factors, and so a biogeographical model of variation is not supported [17,48,61]. Two major lifestyle factors consistently explain the stratification seen in human gut, oral, and skin microbiomes (the vaginal microbiome may be an