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White Paper

The need for standards in human microbiome research

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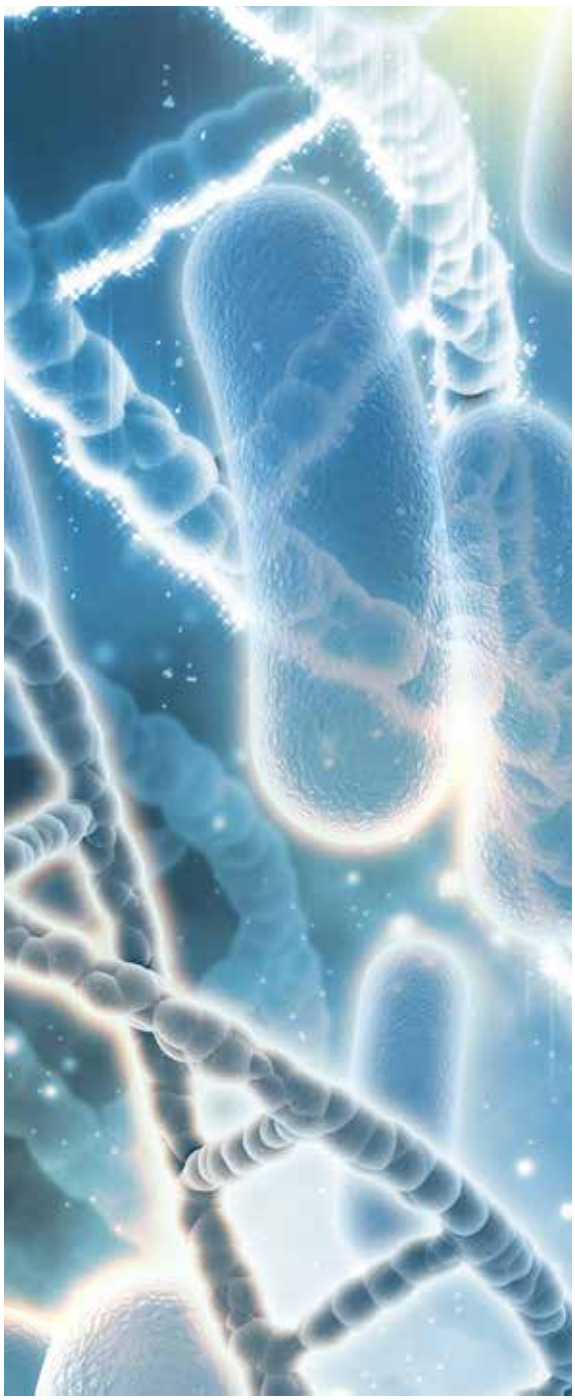

The human body harbors a series of diverse, dynamic microbial communities comprising bacteria, archaea, viruses, and eukaryotes. These communities, collectively termed the human microbiome, play a vital role in human health and disease, particularly with regard to physiology and development, immunomodulation, metabolic regulation, and protection against pathogenic strains[1,2]. By understanding how the human microbiome develops and changes over time with respect to lifestyle and environmental changes or various disease states, and how this in turn affects individual biology, we are offered a powerful tool for personalized healthcare and precision medicine.

Early studies on the human microbiome have been predominantly dependent on microbial cultivation; however, this approach is limited as many microorganisms cannot be cultured *in vitro*[1]. Thus, culture-independent methods for the analysis of microbial communities have been sought out. Accelerated advancements in sequencing have facilitated the use of a metagenomics-based approach for profiling whole microbial genomes directly from their natural environment. This technology has provided further understanding on the genetic potential of microbial communities, how the human microbiome may evolve over time with regard to species abundance and community composition, and how dysbiosis could potentially affect an individual's predisposition to disease.

Though metagenomic studies have offered a wealth of information on the human microbiome, the complexities associated with commonly used methods have posed significant challenges toward assay standardization. Here, bias can be introduced at every stage of a metagenomics workflow, from sample collection, DNA extraction, amplification, library preparation, sequencing, to data analysis[1,3]. Consequently, this bias can obscure the true composition of a microbial community, leading to inaccurate analyses and incorrect conclusions.

One of the primary challenges hindering assay standardization is the limited availability of reference materials. Here, the use of mock microbial communities as controls can help identify issues, determine error rates, and normalize sources of assay bias during sample processing and analysis, in turn improving result interpretation. These mixed communities are typically defined in composition, represent an appropriate level of diversity, and may include a variety of genera sourced on or within the human body, each exhibiting different, relevant phenotypic and genotypic attributes.

To support the need for microbiome reference standards, ATCC has developed ATCC® Microbiome Standards, which are fully sequenced, characterized, and authenticated mock microbial communities comprising genomic DNA or whole cell mixtures prepared from ATCC Genuine Cultures®. In fact, these are the only metagenomics reference materials on the market that are manufactured entirely from validated cultures from ATCC. These products are available with even or stag-

gered abundance, and medium or high levels of mock community complexity ranging from 10 to 20 strains per sample. ATCC® Microbiome Standards enable the optimization of metagenomics workflows and microbiome research applications, providing reliable comparative data while improving assay consistency. The inclusion of these mock community controls throughout a metagenomics study is essential for the identification of potential biases, and can help further elucidate the impact of assay variation on the profiles of microbial communities obtained from microbiome samples.

To further enhance the use of these microbiome standards, ATCC has collaborated with One Codex to combine the power of physical laboratory standards with the leading bioinformatics platform for microbial genomics and metagenomics. Through this collaboration, ATCC has worked in conjunction with One Codex to develop an easy-to-use data analysis module for the ATCC® Microbiome Standards that includes pre-loaded metadata; the ability to analyze both shotgun and 16S rRNA data; automated quality scores assessing true positives, false positives, and relative abundance; and data management, storage, sharing, and graphing capabilities. The combination of the standards and data analysis platform provides an ideal tool for standardizing data from a wide range of sources as well as generating consensus among various microbiome applications and analyses.

Overall, a metagenomics-based approach for profiling the human microbiome has greatly enhanced our knowledge of microbial communities and how these communities affect human health and disease. However, because biases can be introduced throughout the metagenomics workflow, the true species abundance and community composition can be obscured. ATCC® Microbiome Standards combined with the One Codex data analysis platform offer a unique solution for assay standardization and eliminating bias during data analysis. Together, these tools enable you to optimize your metagenomics research applications with confidence, and improve the consistency and reproducibility of your data run after run.

References

1. Committee on Metagenomics: Challenges and Functional Applications. *The New Science of Metagenomics: Revealing the secrets of our Microbial Planet*. The National Academies Press, Washington, DC, 2007.
2. Wang W L, *et al.* Application of metagenomics in the human gut microbiome. *World J Gastroenterol* **21(3)**: 803-814, 2015.
3. Brooks JP, *et al.* The truth about metagenomics: quantifying and counteracting bias in 16S rRNA studies. *BMC Microbiol* **15**: 66, 2015.

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