Microbiome at the Frontier of Personalized Medicine

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CME Activity

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Statement of Need: General internists and primary care physicians must maintain an extensive knowledge base on a wide variety of topics covering all body systems as well as common and uncommon disorders. Mayo Clinic Proceedings aims to leverage the expertise of its authors to help physicians understand best practices in diagnosis and management of conditions encountered in the clinical setting.

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Learning Objectives: On completion of this article, you should be able to (1) give examples of the role of the microbiome in drug efficacy as well as adverse events; (2) critique new studies on treatment efficacy in light of new knowledge gained from the role of the microbiome; and (3) apply knowledge of the microbiome when explaining therapeutic interventions to patients.

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Abstract

The genomic revolution promises to transform our approach to treat patients by individualizing treatments, reducing adverse events, and decreasing health care costs. The early advances using this have been realized primarily by optimizing preventive and therapeutic approaches in cancer using human genome sequencing. The ability to characterize the microbiome, which includes all the microbes that reside within and upon us and all their genetic elements, using next-generation sequencing allows us to now incorporate this important contributor to human disease into developing new preventive and therapeutic strategies. In this review we highlight the importance of the microbiome in all aspects of human disease, including pathogenesis, phenotype, prognosis, and response to treatment, as well as their role as diagnostic and therapeutic biomarkers. We provide a role for next-generation sequencing in both precise microbial identification of infectious diseases and characterization of microbial communities and their function. Taken together, the microbiome is emerging as an integral part of precision medicine approach as it not only contributes to interindividual variability in all aspects of a disease but also represents a potentially modifiable factor that is amenable to targeting by therapeutics.

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The focus of biomedical research for most of its existence has been the ability to identify and target specific disease-associated pathways, leading to therapeutic strategies targeting a pathway. This approach remains mostly naive to interindividual variability in development of disease and response to therapy especially relevant in multifactorial diseases. However, the genomic revolution has provided a window into individual-specific information and its effect on human physiology, paving the way for personalized or precision medicine.[1] Over the past decade, efforts in oncology have allowed human genomic screening to identify a spectrum of germline-encoded sequence variations, enabling individual-specific application of preventive and therapeutic strategies. In addition to personalization of treatment based on genetic contribution to disease pathogenesis, precision medicine efforts have allowed stratification of patients based on response to treatment and development of adverse events.

The advent of microbiome research has identified the microbiome as an important contributor to human health, and in this review we highlight why the microbiome is an integral component of the precision medicine initiative (Figure). The microbiome represents the complex collection of microorganisms both within and upon us, their genomes, and collective functions.[2] The field has benefited vastly from the genomic revolution, allowing DNA-based identification of nonculturable bacteria inhabiting various body sites. Alteration in microbial communities (often referred to as *dysbiosis*) has been shown to be associated with diseases ranging from infectious (*Clostridium difficile* infection) to inflammatory (inflammatory bowel disease [IBD] and rheumatoid arthritis) and metabolic (diabetes and obesity) diseases, suggesting an important role for them in the pathogenesis of multifactorial conditions.[3] An important aspect about the microbiome is its resilience as well as its plasticity, making it more mutable than human cells. Although on first impression these appear opposing concepts, the resilience of the microbiome is evident in health, in which, in spite of temporary insults (travel, diet, antibiotics, etc), the microbiome maintains a relatively stable steady state. In contrast, it represents a malleable organ and can be modified by dietary and other directed therapies (Figure). Furthermore, the interindividual variability in composition and metabolic capacity of the microbiome play an important role in interactions with the environment, resulting in the development of disease as well as response to treatment and development of adverse events. The microbiome has been shown to be determined in part by the host genome, but this contribution seems small when compared with the vast environmental microbiome modulation. Hence, the important role of the microbiome in human health, the interindividual variability and contribution to host function in health, and its plasticity making it a targetable factor all point toward the importance of incorporating the microbiome into precision medicine (Figure).

The current methods use a spectrum of strategies to characterize the microbiome, the simplest being the marker gene approach using variable regions within the highly conserved 16S ribosomal RNA gene. This approach, although valuable in assessing alterations in microbial community structure, fails to provide resolution at species or strain level and does not provide sufficient functional insight into the community. Complimentary approaches including metagenomics (study of all genomes in an ecosystem), metatranscriptomics (characterization of gene expression from all microbes in an ecosystem), metabolomics (characterization of all small molecule metabolites in an ecosystem), and metaproteomics (characterization of all proteins in an ecosystem) provide greater insight into functional potential as well as the expression of microbiome-derived bioactive molecules necessary to understand the therapeutic implications for the microbiome. Although the microbiome represents an attractive target for the development of personalized treatment approaches, standardization of methods to develop reliable and reproducible microbiome-based diagnostic and therapeutic strategies remains a challenge. The strong effort by the scientific community, as well as collaboration with rapidly emerging biotech companies, provides an optimistic outlook for developing microbiome-dependent and microbiome-targeted diagnostics and therapeutics.

SEQUENCING REVOLUTION ALLOWS DEVELOPMENT OF PRECISE MICROBIAL DIAGNOSTICS

Awareness of the role of the microbiome in health has both benefited from and been spurred by sequencing technology. Once considered milestone achievements requiring

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