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*Commentary*

# Decoding Microbiome Research for Clinical Psychiatry

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It is remarkable to see how fast and furious microbiome research over the past decade has advanced to the forefront of neuroscience and psychiatry. From an insider's perspective, there are several reasons to consider the microbiome in clinical psychiatry: (1) to identify biomarkers related to biological differences that allow us to identify subgroups of clinical populations and improve the ability to match individuals to the best treatment, (2) to identify individuals at risk for early intervention, (3) to provide novel targets for drug development, and (4) to facilitate the expansion and new development of microbiome-targeted therapies including, but not limited to, diet, prebiotics, and probiotics. An individual's microbiome is their own, and the colonization of all surfaces of our body that begins at birth continues through early life. The diversity, composition, and function of an individual's microbiome are influenced early in life by mode of delivery, breast milk versus formula, exposure to antibiotics and nonantibiotic drugs, sex, diet, stress, housing conditions, and geography.[1] Our own genetics influences our microbiome, and gene–environment interactions over life influence the microbe–host interactions that impact host physiological processes. Advances in our understanding of the microbiome in health and disease are promising. Media, public, academics, and health-care providers are challenged to understand this dynamic area of research and to implement best practices to improve treatment approaches in mental health. In a recent issue of *The Canadian Journal of Psychiatry*, Butler et al. provide an excellent overview of recent microbiome research and advice on best practices in clinical psychiatry related to the microbiome.[2]

For neuroscience and psychiatry, a few key studies using germ-free mice provided the spark for neuroscientists to consider how microbes may influence brain function.[3-6] As additional neuroscientists considered the microbiome, new results demonstrated that the microbe–host interactions and signaling of the microbiota–gut–brain axis influence neurodevelopment, neuroplasticity, neurotransmitter systems, neurogenesis, many behavioral phenotypes, and more.[7] Based on this preclinical work, interest in understanding a role for the microbiome in clinical psychiatry has recently emerged. As reviewed in the study of Butler et al., alterations in microbiota composition have been reported in major depressive disorder, bipolar affective disorder, anxiety disorders, schizophrenia and psychotic disorders, neurodegenerative disorders, and autism spectrum disorder.[8] While differences between diagnostic groups and healthy volunteers have been observed, identifying key taxa and the functional microbial pathways that influence host physiology is an essential step to advance the translation of microbiome research to clinical applications. To date, many studies have relied on 16S rRNA gene sequencing and analytical tools that limit the specificity of taxa identified resulting in poor reproducibility of health-related bacterial taxa across studies. 16S rRNA sequencing only identifies taxa to the genus level and provides no direct insight into the functional changes of microbiota that may be driving effects on host physiology. Additional approaches include shotgun metagenomics and metabolomics. Shotgun metagenomics sequencing provides not only who is there but gives functional readouts of bacterial metabolism. Metabolomics examines the metabolites of the bacteria and/or the host. As noted in the study of Butler et al., short chain fatty acids (SCFAs) are important bacterial metabolites produced by gut bacteria that influence other commensals and are important to gut physiology as well as part of microbiota–host signaling systems that extend beyond the gut.[9] Beyond SCFAs, microbially derived molecules include neurotransmitters, indoles, bile acids, choline metabolites, lactate, and vitamins, and evidence is accumulating that the microbial metabolites may

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contribute to the pathophysiology of psychiatric illness (e.g., in depression[10]).

An important consideration related to the microbiome, noted in the study of Butler et al., is the high interindividual variability. Notably heterogeneity is a hallmark of psychiatric disorders, and the potential of the microbiome and microbiome-related biomarkers to help identify subtypes of patients within diagnostic areas is promising. An additional important consideration that is noted in the study of Butler et al. is the relationship between drugs and the microbiome. While most individuals are aware that antibiotics impact the microbiome, it is important to note that nonantibiotic drugs also impact microbiome composition and function.[11] These effects can be transient in nature or have long-lasting effects if used for an extended period of time. Understanding how all drugs influence our microbiome is important but also understanding how our microbiome influences drug metabolism, drug efficacy, side effects, and treatment response is essential for successful precision medicine approaches.

The public is engaged and interested in the microbiome that increases the need for clinicians to better understand whether microbiome-targeted therapies can help in psychiatry and to establish best practices for their use in their patients. Butler et al. provide a good overview of the clinical evidence to date for the benefit of probiotics in healthy individuals and in clinical populations. Table 3 provides a list of specific bacterial taxa that have been shown to have a benefit on mood. Deciphering this list and matching these taxa to the commercially available products is challenging. In Canada (www.probioticchart.ca) and in the United States (usprobioticguid.com), a clinical guide to probiotic products is an excellent resource for clinicians and their patients to use. These guides overview the evidence that supports the use of commercially available products across a wide range of medical conditions. In addition, as noted by Butler et al., the International Scientific Association for Probiotics and Prebiotics (isappscience.org) has infographics and resources related to probiotics, prebiotics, and fermented food for consumers, scientists, and clinicians. In parallel, with these products other microbiota-targeted therapeutic approaches may have utility in clinical psychiatry. For example, nutritional psychiatry and the importance of diet to mental health is gaining momentum.

Overall, evidence in healthy and clinical populations show that microbes influence brain function and behavior. Much of the work to date has examined gut microbiome composition, and more studies are needed that utilize functional readouts such as metagenomics and metabolomics. Active studies continue to add to our knowledge of how genes and environment influence microbiota–brain interactions in mental health. Butler et al. provide an excellent overview of the field; it will be exciting to see the opportunities for microbiota-based therapeutics develop further and the application of microbiome–host-related biomarkers in precision medicine approaches.

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