# COMPELLING COMMENTS

## Integrating Metagenomics into Personalized Medicine in Dermatology

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**ABSTRACT**

There has been a recent focus on the association between human microbiomes and disease development, disease resistance, and therapy response. Fecal transplants for inflammatory bowel disease and resistant *Clostridium difficile* infection have demonstrated that manipulating the gut microbiome can be beneficial in treating disease. In dermatology, response to immune checkpoint inhibitors for melanoma therapy are affected by differences in gut microbial composition. Bleach baths, which alter the skin microbiome, improve atopic dermatitis. Gut dysbiosis, or disturbance of the gut microbiome in early life, have been shown to influence the development of systemic sclerosis and atopic dermatitis. Metagenomic sequencing can therefore be a useful addition in personalized medicine to identify therapy responders versus non-responders, patients at risk of serious side-effects from biologics and immune checkpoint inhibitors, and prebiotic supplements that aid in improving therapy. response.

Recent articles in high-impact scientific journals have examined the complex relationship between human microbiomes and systemic diseases. Terms such as the "gut-brain-skin axis", "gut-joint axis", and similar iterations, have redefined the context at which we approach disease – that is, not by examining and treating a condition solely from the perspective of the damaged organ or gene, but by understanding how the organ functions or malfunctions in relation to other, seemingly unrelated, biological systems. These systems include the skin and gut microbiomes. Metagenomics seeks to expand our understanding of the genetic composition of microbiomes and the crosstalk between bacterial communities and host environment. The integration of metagenomics into personalized medicine in dermatology, which currently does not scrutinize beyond a patient's genetic content, can be a welcome addition to the arsenal of "-omics" available in assessing a patient's predicted response to treatment.

Disturbance of both the skin and gut microbiomes in early life, called "dysbiosis", is associated with the development of inflammatory and autoimmune skin disorders, such as psoriatic arthritis,[1] atopic dermatitis,[2-5] and systemic sclerosis.[6] Studies have shown that altering the microbial composition of a microbiome, such as by fecal transplant in inflammatory gut disorders or by bleach baths in atopic dermatitis, can improve disease resistance and therapy response. The emergence of cancer immunotherapy with immune checkpoint inhibitors, targeting cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1), has prompted research into the

differences of gut microbiota between responders and non-responders to therapy.

Three papers published in *Science* have found that the gut microbiome is a major factor in tumor response modulation, in melanoma patients treated with checkpoint inhibitors.[7-9] Sivan *et al.* found that melanoma growth was significantly different in two groups of mice harboring distinct gut microbiota, a difference which was eliminated upon cohousing or after fecal transfer from one mouse group to another.[8] Similarly, gavage with a specific, gut-associated bacteria restored adequate T-cell response in antibiotic-treated and germ-free mice treated with CTLA-4 blockade, in a paper by Vétizou *et al*.[9] Transitioning to human studies, Gopalakrishnan *et al*. used metagenomics to identify significant differences in the diversity, composition, and function of the gut microbiome of responders versus nonresponders to PD-1 blockade.[7] Murine studies confirmed that a "favorable" gut microbiome can lead to enhanced antitumor immunity and smaller tumor size after immune checkpoint blockade.

Which types of bacteria comprise this "favorable" microbiome? Vétizou *et al.* suggested an antitumor role of *Bacteroides fragilis* in CTLA-4 blockade.[9] *Bacteroides* is also associated with resistance to checkpoint blockade-induced colitis in melanoma patients.[10] Other favorable bacteria included various species of *Bifidobacterium*[8], *Coprococcus*[1], *Ruminococcus*[1], and *Akkermansia*.[11] Of note, *Ruminococcus* was protective against the development of IgE-associated eczema in infants.[3] Multiple mouse studies have documented the specific effects of each bacterial group in maintaining immune homeostasis, including TNF production, enhanced dendritic cell activation, and stimulating the differentiation of Th17 cells to Th1 cells.[12]

In these studies, metagenomic shotgun sequencing of patient stool samples was essential in identifying the microbial composition of responders versus non-responders, as well as identifying microbes that are potentially protective against disease. Although there were discrepancies over which microbial groups were considered favorable, the addition of metagenomics data in anti-cancer personalized medicine could significantly improve decision-making in drug choice and side-effect prevention. Metagenomic sequencing could even be expanded to identify responders versus non-responders to biologics in dermatology. Once we have an understanding of which microbes are beneficial to therapy, the next step is to customize a cocktail of probiotics that can be administered to augment treatment and to develop an effective mode of delivery.

In its current state, metagenomics is overshadowed by the enigma of our own genome – how can we possibly begin to understand the genetics of other organisms when we can barely comprehend that of our own? Identification of the most favorable microbial composition would require an expansive human database correlating different bacterial species with clinical response.[13] In addition, microbiomes can differ among age groups in certain dermatological conditions, such as in pediatric versus adult atopic dermatitis.[14] Microbial delivery and engraftment into the host microbiome are other hurdles to overcome. In the clinical setting, the concomitant use of antibiotics and immunomodulators in melanoma and inflammatory or autoimmune skin disorders complicates the use of metagenomic analysis. Despite these shortcomings, the

success of fecal transplant in the clinical setting has demonstrated that manipulating the gut microbiome can provide significant benefits to the patient.

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