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EDITORIAL

Bringing gut microbiota into the spotlight of clinical research and medical practice

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Abstract

Despite the increasing scientific interest and expanding role of gut microbiota (GM) in human health, it is rarely reported in case reports and deployed in clinical practice. Proteins and metabolites produced by microbiota contribute to immune system development, energy homeostasis and digestion. Exo- and endogenous factors can alter its composition. Disturbance of microbiota, also known as dysbiosis, is associated with various pathological conditions. Specific bacterial taxa and related metabolites are involved in disease pathogenesis and therefore can serve as a diagnostic tool. GM could also be a useful prognostic factor by predicting future disease onset and preventing hospital-associated infections. Additionally, it can influence response to treatments, including those for cancers, by altering drug bioavailability. A thorough understanding of its function has permitted significant development in therapeutics, such as probiotics and fecal transplantation. Hence, GM should be considered as a ground-breaking biological parameter, and it is advisable to be investigated and reported in literature in a more consistent and systematic way.

Key Words: Gut microbiota; Biomarker; Fecal microbiota transplantation; Dysbiosis; Prebiotics

Core Tip: Gut microbiota (GM) serves as a multifaceted tool in healthcare, acting as a potential biomarker, diagnostic, prognostic, and therapeutic entity. While dysbiosis is linked to various diseases, harnessing microbiome's diagnostic potential introduces challenges due to its variability and complex identification techniques. As a prognostic tool, GM provides insights into an individual's health status and disease risks, influencing treatment outcomes. Moreover, it emerges as a therapeutic pathway, with interventions such as prebiotics and fecal microbiota transplantation showing promise. Despite growing recognition, its integration into clinical practice remains limited, necessitating increased research, educational initiatives, and collaborations, to unlock the full potential of GM in advancing patient care.

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INTRODUCTION

Although scientists have long been aware of the presence of microorganisms in the human digestive system, since the era of Antonie van Leeuwenhoek in the 17th century, gut microbiota (GM) gained significant momentum and understanding in the late 20th and early 21st centuries. The first reports on GM appeared in literature in 1984, with a frequency of one publication *per* year. The development of advanced DNA sequencing technologies in the late 20th cen-tury contributed to better identifying the diverse array of microbes in the gut. Today, it is a widely discussed and in-creasingly popular indicator. With growing age, factors like host genetics, dietary changes, antibiotics, and stress gra-dually affect the composition of GM-a phenomenon known as dysbiosis[1]. Dysbiosis is associated with the development and outcomes of various pathologies, including inflammatory bowel diseases (IBD)[2], neurodevelopmental disorders[3], breast cancer[4], colorectal cancer (CRC)[5] *etc.* Over the past years, light has been shed on the role of microbiome in therapeutic approaches for the above health conditions. In 2007, the National Institutes of Health in the United States initiated the Human Microbiome Project, aiming to characterize the human microbiome and understand its role in health and disease.

This editorial emphasizes on the crucial role of microbiome, highlighting its recognition not just as a secondary endpoint but as a primary focus in clinical cases and trials, aiming to raise awareness, spark discussions and encourage a collective effort within the medical community to better understand and leverage the microbiome's significance, ultimately enhancing patient care and scientific knowledge.

GM AS A BIOMARKER

A biomarker is a well-defined characteristic that serves as an indicator of biologic processes, either physiologic or pathologic, or as a measure of response to an exposure or intervention[6]. Biomarkers are objectively measurable variables, well-known for their specificity and sensitivity over a specific biologic process. Several categories of biomarkers have been established based on their potential uses. For instance, a diagnostic biomarker is utilized to identify or validate the existence of a particular disease or medical condition, or to pinpoint an individual with a specific disease subtype[7]. These biomarkers can serve the purpose of identifying individuals with a disease as well as of redefining the categorization of the disease[8].

Dysbiosis is associated with various pathological conditions, both intestinal and extra-intestinal[9]. Hence, GM has been proposed as a biomarker for various conditions[10-14]. For example, some metabolites produced by gut bacteria, such as short-chain fatty acids (SCFAs), can be used as diagnostic markers for cardiovascular diseases[15]. SCFAs, such as butyrate, have also been studied as a potential biomarker for patients with pancreatic cancer. Evidence suggests that SCFAs can modulate several processes associated with pancreatic cancer development, including inflammation, cell proliferation, and immune responses[16]. Moreover, fecal microbes and butyrate have been suggested as biomarkers in order to distinguish patients with pancreatic ductal adenocarcinoma from patients with autoimmune pancreatitis and healthy subjects[17]. However, its use as a biomarker is still in the early stages of development. Further studies are needed to standardize its use in clinical practice and to establish clear causative relationships between GM composition and specific diseases. What makes GM a challenging biomarker is its variability and complexity as its composition can vary significantly among individuals[18]. Another important factor is the sophisticated techniques needed to identify and characterize GM. Collecting and analyzing samples can involve invasive procedures requiring special expertise and equipment. This can render the utilization of GM as a biomarker in routine clinical settings quite challenging.

GM AS A DIAGNOSTIC TOOL

GM has the potential to serve as a valuable diagnostic tool for various health conditions[19]. For instance, individuals suffering from Crohn's disease often exhibit a reduced diversity and overall imbalance in GM. This encompasses a

diminished variety within the *Firmicutes phylum* and reduced levels of *Faecalibacterium prausnitzii*[20]. Furthermore, according to a recent study, GM could be used as a non-invasive way to diagnose membranous nephropathy[21]. In the same study, a diagnostic model was developed, which demonstrated an excellent identification capability with an area under curve (AUC) of 98.36%, in a standard sensitivity-specificity receiver operating characteristic curve analysis. This model was based on seven operational taxonomic units of the microbiome. Additionally, the involvement of GM in the onset of the disease was highlighted. Changes in GM have also been linked to CRC in various populations, and numerous bacterial species have been found to contribute to tumorigenesis[22]. Through a comprehensive analysis of 526 metagenomic samples from Chinese, Austrian, American, German and French cohorts, researchers identified seven enriched species (*Bacteroides fragilis, Fusobacterium nucleatum*, *Porphyromonas asaccharolytica*, *Parvimonas micra*, *Prevotella intermedia*, *Alistipes finegoldii*, and *Thermanaerovibrio acidaminovorans*) and 62 depleted species in CRC cases compared to controls. Their findings also support the effective performance of these seven CRC-enriched bacteria in distinguishing CRC patients from controls across different cohorts[22]. A decrease in gut *Firmicutes*, including *Faecalibacterium prausnitzii* and *Roseburia sp*. has been noticed in patients with IBD[23]. Reduction in *Firmicutes* may lead to increased local inflammation by reducing anti-inflammatory cytokines. Additionally, it could potentially result in impaired colonic barrier function due to a deficiency in SCFAs[23]. In an assessment of GM as a diagnostic tool, a machine learning approach utilizing generalized linear models with penalized maximum likelihoods was employed. The microbial composition showed a better IBD/irritable bowel syndrome predictive accuracy [mean AUC of 0.91 (0.81-0.99)] than the currently used fecal inflammation biomarker calprotectin [mean AUC of 0.80 (0.71-0.88), $P = 0.002$][24].

However, there are some challenges to overcome in order to clarify the diagnostic potential of GM. The inter-individual variability of GM and the overlap of disrupted microbiota communities among multiple diseases, pose significant obstacles in using taxonomic data for diagnosis and disease characterization[19]. Standardization of methods and distinguishing causation from correlation are also important challenges. Nevertheless, advances in metagenomic sequencing [25], machine learning[26], and multi-omics approaches[27] are helping to identify more specific microbial markers in gut associated with various diseases.

GM AS A PROGNOSTIC TOOL

Analyzing the composition and function of GM can provide insights into an individual's health status and the risk of developing specific diseases such as Crohn's disease[28], gestational diabetes[29], coronary artery disease[30] and celiac disease[31]. Notably, research has demonstrated that GM can forecast both clinical course of patients and their response to particular treatments including those for cancers[32], *Clostridioides difficile* infection[33], rheumatoid arthritis[34], bariatric surgery[35] and IBDs[36]. For example, Shi *et al*[37] suggested that GM and pathway markers identified in their study may function as a predictive tool for identifying patients with rectal cancer who are likely to benefit from neoadjuvant chemoradiotherapy (nCRT)[37]. Furthermore, the presence of members of the *Bacteroidales* order, such as *Parabacteroides merdae*, was found to be more prominent in non-responders while increased activity in fatty acid metabolism and propionate metabolism pathways seemed to improve effectiveness of anti-tumor treatment[37]. They also suggested that GM could be harnessed for identifying patients who have a lower risk of experiencing diarrhea associated with nCRT[37]. This signifies that microbiota-based medicine has the potential to predict and mitigate the adverse effects of specific medications. In this context, it has been found that GM of patients who will experience weight gain after chemotherapy differed from that of those who will not[38]. Therefore, if responsiveness to treatments can be predicted by pre-screening patients' microbiota, management can be tailored to meet individual needs and determine whether some patients are good candidates for a certain treatment[39].

Yamaoka *et al*[40] found that assessing the levels of *Fusobacterium nucleatum* could serve as a predictive factor of clinical outcomes in patients with CRC[40]. High abundance of *Fusobacterium nucleatum* in colorectal tumors was also associated with poorer overall survival (OS)[41]. Concerning hepatocellular carcinoma, the *Prevotella/Bacteroides* ratio has the potential to serve as a prognostic indicator for the response to nivolumab treatment. A higher ratio is associated with more favorable treatment efficacy[42]. Also, survival analysis demonstrated that patients with increased levels of species *Lachnospiraceae bacterium*-GAM79, *Erysipelotrichaceae bacterium*-GAM147, *Ruminococcus callidus*, *Alistipes megaguti*, and *Bacteroides zoogleoformans* had extended progression-free survival and OS[43]. Even in organ transplantation, GM of both donor and recipient can impact the prognosis and success of the procedure[44]. The composition of GM could additionally function as a predictive marker for the severity of a disease by modulating immune responses[45]. Specifically, when examining the microbial species linked to the severity of corona virus disease 2019 (COVID-19) infection, a negative correlation between disease severity and *Faecalibacterium prausnitzii* and *Bifidobacterium bifidum* was observed. Composition of GM in patients with COVID-19 is also concordant with the plasma levels of various inflammatory cytokines, chemokines and markers of tissue damage[45].

Finally, GM may impact an individual's vulnerability to infectious diseases. In this context, researchers have emphasized the significance of identifying the microbiome of patients admitted to the intensive care unit as a key strategy for averting hospital-acquired infections[46].

GM AS A THERAPEUTIC TOOL

In addition to serving as a diagnostic and predictive marker, GM is being explored as a potential therapeutic tool in various medical contexts. It has been shown that GM can influence an individual's response to a medical treatment by

altering its bioavailability, bioactivity and toxicity[47]. As discussed above, GM could be used to predict responses to various therapies including chemotherapies and immunotherapies. Moreover, interventions have been designed to manipulate or modify the composition and function of GM in order to improve outcomes. Interventions that aim to restore microbial balance in the gut include prebiotics, probiotics, synbiotics, and fecal microbiota transplantation (FMT). Prebiotics are non-digestible fibers and compounds found in certain foods that promote the activity and growth of beneficial bacteria in the gut[48] while probiotics are alive microorganisms, mainly bacteria and yeast, that confer health benefits to the host by positively modulating gut microflora and reducing pathogenic bacteria releasing toxic compounds in human gut[49]. Synbiotics refer to a mixture of prebiotics and probiotics[50]. Such interventions can be used for treating *Costridium difficile* infection, IBD, and other gastrointestinal disorders[51]. They can also be employed in the field of cancer immunotherapy to enhance the effectiveness of cancer treatments[52]. For instance, interventions aimed at manipulating the GM and promoting SCFA production, such as probiotics, prebiotics, and dietary fiber supplementation, have demonstrated promise in altering the tumor microenvironment and improving the effectiveness of immunotherapy[53]. In a mouse model, the positive impact of microbiota was transferable through FMT. Specifically, introducing stool from responsive donors to germ-free mice resulted in an immune-mediated anti-tumor response[54]. Moreover, FMT can be applied in allergies and autoimmune disorders to either prevent or alleviate allergic reactions and autoimmune conditions. For instance, some early studies have suggested that there are differences in the GM profile of individuals with food allergies (FAs) compared to individuals without FAs, and that FMT could be a promising strategy to prevent allergic symptoms[55]. FMT could also enhance clinical remission, clinical response, and endoscopic remission in individuals with ulcerative colitis, as well as promote clinical remission in those with Crohn's disease[56]. Furthermore, probiotic supplementation has been found to improve subjective sleep quality as measured by the change in Pittsburgh sleep quality index score[57]. In the years ahead, researchers will be capable of leveraging pharmaco-microbiomics, the field of study that seeks to uncover the impact of the microbiome on drug metabolism, efficacy and toxicity, for personalizing medical treatments, optimizing drug therapies, and reducing adverse effects.

CURRENT STATUS IN LITERATURE AND CLINICAL PRACTICE

GM is increasingly recognized as a significant endpoint in studies. However, upon analyzing their distribution, a notable pattern of predominance of reviews emerges. Only a modest 4% corresponds to clinical studies and clinical trials, and merely 0.35% pertains to case reports. This indicates a conspicuous scarcity of data pertaining to GM in the context of patient-related scenarios. Regrettably, the current application of GM in research appears mostly theoretical, serving as bibliographic knowledge, with limited incorporation into everyday medical practice. This discrepancy arises mainly from two factors. Firstly, there is a notable absence of familiarity with GM indices in clinical practice. Additionally, a substantial proportion of healthcare professionals lack the required background to measure and evaluate these indices.

A frequently posed question revolves around the methodologies employed for studying GM and the feasibility of conducting such analyses within a laboratory setting. Various techniques are utilized to collect samples for evaluating GM, with common sources encompassing fecal samples, samples obtained through endoscopy and samples derived from biopsies. Following sample collection, standard analytical methods involve genomic DNA extraction, amplification of the 16S rRNA gene, sequencing and subsequent bioinformatic analysis of sequencing data[58]. Notably, the 16S rRNA gene and sequencing methodology have garnered extensive utilization. This culture-free approach provides a way to identify and compare bacterial diversity within intricate microbiomes or environments that present challenges for traditional study methods. The employment of this method enhances the capacity to gain valuable insights into composite microbial colonies[59]. 16S rRNA gene sequencing is a culture-independent method, enabling the identification of bacteria that may be challenging to culture or have not been previously characterized[1]. Therefore, this approach facilitates a comprehensive and culture-free exploration of the intricate microbial composition present in diverse environments, such as the complex ecosystems within the human gut.

Despite its fundamental significance as a biomarker, the utilization of GM in this capacity is not as prevalent as that of other frequently referenced markers, such as gender, age, Body mass index, race, smoking habits, and profession, which are universally acknowledged as pivotal factors influencing various pathologies. The consistent reference to these markers underscores their recognized impact on health conditions. Conversely, awareness regarding the association of GM with conditions such as breast cancer or IBD might be less pervasive. This discrepancy is attributable to the extensive and historical use of certain markers like smoking, while the microbiome is a relatively novel consideration. Therefore, the inclusion of microbiome analysis, even as a secondary outcome, is highly desirable. Such inclusion not only broadens baseline knowledge but also contributes to establishing the microbiome's standing in the conscience of the broader medical community, ensuring that a larger readership is well-informed about its relevance and potential implications.

While the integration of GM into medical research is gaining momentum, challenges persist in establishing it as a widely recognized biomarker[60]. The dynamic nature of the microbiome and its relatively recent emergence in scientific discourse contribute to its slower adoption compared to traditional markers. Efforts to bridge this gap involve emphasizing the microbiome's relevance to secondary outcomes[61], thereby enriching the understanding of its intricate connections with health. Researchers are increasingly delving into the complexities of GM to uncover its potential implications for various health conditions[62]. As the scientific community continues to explore and unravel the mysteries of the microbiome, collaborative initiatives are essential to promote its integration into mainstream medical considerations and pave the way for more targeted and holistic approaches to healthcare.

GM should be incorporated as a biomarker in case reports, assuming the role of a routinely integrated indicator in daily clinical practice. Ideally, healthcare practitioners should develop an automated incorporation of GM-related know-

ledge into the overall clinical assessment of the patient, as it occurs with established factors. Moreover, the implementation of GM as a biomarker in case reports would allow for the documentation of challenges and deficiencies that may arise with regards to its utilization, thereby offering valuable feedback for targeted research and subsequent refinements. This approach ensures that the outcomes and implications of integrating GM into case reports are widely disseminated, fostering increased awareness, and encouraging more medical centers to adopt its inclusion on a comprehensive scale.

In this paradigm shift towards incorporating GM as a routine biomarker in case reports, the integration process should extend beyond clinical practice to encompass educational initiatives within medical training programs. Educating healthcare professionals about the intricacies of GM and its potential impact on health outcomes is paramount for successful integration. Developing specialized training modules and incorporating GM-related knowledge into medical curricula would empower future practitioners to understand and utilize this biomarker effectively. By fostering a comprehensive understanding of GM, medical professionals can confidently incorporate it into their clinical assessments, contributing to a more holistic approach. This educational integration ensures that the next generation of healthcare providers is well-equipped to navigate the complexities of the microbiome landscape, further solidifying its place in routine clinical practice.

SUGGESTIONS FOR IMPROVED INCORPORATION

A pivotal consideration is the integration of GM into routine clinical practice, but this mandates a circumspect and evidence-driven approach, which at the moment cannot be corroborated by existing literature, despite current promising and valuable insights. Therefore, incorporation of GM into research is necessary in order to improve reliability and applicability in healthcare decision-making. Illustrative case studies detailing scenarios wherein comprehension of GM proves pertinent to diagnosis, treatment or management, could serve as a robust argument for the incorporation of microbiome knowledge in clinical practice.

Given the necessity to integrate GM into routine clinical practice, it becomes evident that a collaborative effort among researchers, healthcare professionals, and policy makers is essential. Creating interdisciplinary teams that involve microbiologists, clinicians, and experts in healthcare policy could accelerate the translation of GM research findings into actionable guidelines for clinical settings. This collaborative approach ensures that the incorporation of GM into routine practice aligns with evidence-based standards and regulatory frameworks. By fostering synergy across different domains, this concerted effort strives to establish a robust foundation for the seamless integration of GM into everyday healthcare decision-making.

Potential avenues for increased utilization reside in incorporating GM assessments more frequently within patient research protocols and clinical trials. This approach offers a platform to comprehensively evaluate the method's advantages and disadvantages, thereby presenting opportunities to address challenges and refine methodologies in subsequent targeted research endeavors[63]. In summary, the exploration of GM within the framework of clinical trials yields valuable insights into disease mechanisms, treatment responses, and overall health outcomes. As our understanding of the microbiota is continuously expanding, its integration into clinical research gains escalating importance for the advancement of medical knowledge and the enhancement of patient care.

By systematically integrating GM assessments into clinical trials, researchers gain valuable insights into the dynamic interplay between the microbiota and various health conditions. This approach not only allows for the identification of potential biomarkers and therapeutic targets but also provides opportunities to address challenges and refine methodologies. The continuous expansion of our understanding of the microbiota underscores the escalating importance of its integration into clinical research. Leveraging GM data in clinical trials holds promise for the development of more targeted and effective interventions, contributing to a paradigm shift in healthcare towards personalized and precision medicine.

Another important objective would be improving healthcare practitioners' familiarization with GM. This would empower doctors to provide more comprehensive and individualized care. Provision of educational resources that would bridge the gap between the emerging field of microbiome research and clinical practice could facilitate this objective. Organizing conferences, workshops, and symposia that bring together experts in microbiome research and healthcare professionals could be a great adjunct. Moreover, establishing partnerships could facilitate the translation of research findings into clinical applications and help doctors stay informed about relevant developments.

In tandem with enhancing healthcare practitioners' familiarity with GM, fostering a culture of continuous learning is essential. Developing specialized training programs within medical curricula and professional development courses can provide a structured approach to GM education. Integrating microbiome-related content into medical training modules ensures that future healthcare professionals are well-equipped with the necessary knowledge and skills. Furthermore, leveraging online platforms and digital resources can enhance accessibility, allowing practitioners to stay updated on the latest developments in GM research at their own pace. By cultivating a learning environment that encourages ongoing education and professional growth, the medical community can effectively navigate the complexities of integrating GM insights into routine clinical practice, ultimately facilitating more personalized and informed patient care.

CONCLUSION

Once overlooked, GM has emerged as a pivotal player in health and disease. Dysbiosis, influenced by factors like genetics, diet, antibiotics and stress, is associated with various pathologies, emphasizing the dynamic nature of the gut

microbial ecosystem. GM shows promise as a diagnostic tool, with potential applications in identifying and categorizing diseases. Its role extends beyond diagnosis, and studies now demonstrate its prognostic significance, as well as its therapeutic role in benign and malignant conditions. While GM is increasingly explored, challenges include inter-individual variability, method standardization, and distinguishing causation from correlation. Future research directions should involve leveraging advances in metagenomic sequencing, machine learning, and multi-omics approaches to identify specific microbial markers associated with various diseases. Given the surprisingly wide variety of conditions and purposes where GM's usefulness emerges, GM should ideally be routinely examined and reported in clinical case reports as well as in comparative studies.

FOOTNOTES

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