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Review paper

Genomics in Personalized Medicine with Microbiome Approach

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Abstract

Background and aim: The genomic revolution has paved the way for incorporating a vast amount of personalized information into clinical practice, leading to a transformative impact on medicine and science. The gut microbiome, often referred to as our "second genome," acts as a dynamic interface between the host and its environment, influencing both health and disease risk.

Methods: In this review, we provide a summary of how personalized characterization of microbiome composition and function can contribute to personalized diagnostic assessments, risk stratification, disease prevention, treatment decision-making, and patient follow-up. We also address the limitations, challenges, and potential pitfalls that arise when integrating patient-specific microbial data into clinical practice. The field of microbiome research faces unique challenges and we discuss these challenges to highlight the need for further research and development in this area.

Results: Nutritional interventions and the use of pre-, pro-, and post-biotics offer promising avenues for personalized manipulation of the microbiome. These insights hold the potential to develop individualized approaches that harness the microbiome as a central target in precision medicine.

Conclusion: In conclusion, the integration of personalized microbiome characterization into clinical practice has the potential to revolutionize healthcare. By leveraging the vast amount of information provided by the microbiome, we can enhance diagnostic accuracy, improve risk assessment, refine treatment decisions, and optimize patient care. However, addressing the challenges and limitations in this field is crucial to unlock the full potential of the microbiome as a precision medicine target.

Keywords: *Genomics, Personalized medicine, Microbiome*

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Introduction

In recent years, the fields of genomics, personalized medicine, and microbiome research have witnessed remarkable advancements, revolutionizing our understanding of human health and disease. Genomics, the study of an organism's complete set of genetic material, has provided invaluable insights into the intricacies of our genetic makeup and its role in various aspects of biology and medicine. Concurrently, the human microbiome, consisting of trillions of microorganisms residing within and on our bodies, has emerged as a key player in shaping our health and influencing disease processes [1].

Personalized medicine, a patient-centric approach to healthcare, recognizes the individuality of each person and seeks to tailor medical treatments and interventions based on their unique characteristics. By leveraging genomic information, healthcare providers can gain insights into an individual's genetic predispositions, predict disease risk, and make informed decisions regarding treatment selection and disease prevention [2].

However, recent research has unveiled the significant impact of the human microbiome on health and disease, prompting a paradigm shift in personalized medicine. The microbiome, encompassing a diverse array of microorganisms such as bacteria, viruses, fungi, and archaea, plays a crucial role in maintaining homeostasis and influencing various physiological processes. It has been implicated in the development and progression of numerous diseases, including gastrointestinal disorders, autoimmune conditions, metabolic disorders, and even mental health conditions [3].

The integration of genomics and the microbiome in personalized medicine represents a promising approach that holds the potential to revolutionize patient care. By combining genomic information with an in-depth understanding of an individual's microbiome composition and function, researchers and clinicians can unravel the intricate interplay between our genetic makeup and the microorganisms that inhabit our bodies. This integration allows for a more comprehensive understanding of an individual's health status, disease risk, and treatment response, leading to personalized strategies for diagnosis, treatment, and disease prevention [4].

This review article aims to provide a comprehensive overview of the field of genomics in personalized medicine, with a specific focus on the microbiome. It will explore the impact of genomics on personalized medicine, highlighting its role in disease diagnosis, treatment selection, disease prevention, pharmacogenomics, and precision oncology. Additionally, the review will delve into the significance of the microbiome in personalized medicine, discussing its potential applications in disease diagnosis and risk assessment, precision antibiotic therapy, microbiome-based therapies, and personalized nutrition.

While the integration of genomics and the microbiome in personalized medicine holds great promise, it also presents challenges and limitations. Standardization of microbiome profiling methods, establishing causal relationships between microbial dysbiosis and disease, and ensuring the safety and efficacy of microbiome-based interventions are among the hurdles that need to be addressed. Nonetheless, the transformative potential of microbiome-based personalized medicine is undeniable, warranting further research, collaboration, and the translation of findings into clinical practice [5].

Genomics

Genomics is the study of an organism's complete set of genetic material, encompassing the analysis of genes, non-coding regions, and regulatory elements. It involves techniques such as DNA sequencing and bioinformatics to unravel the structure, function, and relationship between genes, providing valuable insights into biology, medicine, and various other fields.

The human microbiome refers to the collection of microorganisms, including bacteria, viruses, fungi, and other microorganisms, that live within and on the human body. These microorganisms are found in various parts of the body, such as the skin, mouth, gut, and reproductive organs. The human microbiome is incredibly diverse, with trillions of microorganisms living in symbiosis with the human host [6].

Human Microbiome

The human microbiome, consisting of trillions of microorganisms residing in and on our bodies, has emerged as a key player in human health and disease. Recent advances in microbiome research have uncovered its profound influence on various aspects of our physiology, including metabolism, immune function, and even mental health. The growing recognition of the microbiome's role in health has paved the way for the development of personalized treatment approaches that leverage the unique characteristics of an individual's microbiome [7].

Personalized medicine, on the other hand, is an approach to healthcare that considers an individual's unique genetic makeup, environment, and lifestyle factors to tailor medical treatments and interventions. It recognizes that each person is different and that a one-size-fits-all approach may not be optimal for everyone.

Advancements in microbiome research have opened up new possibilities for personalized medicine. By analyzing an individual's microbiome composition and understanding its interactions with the body, healthcare professionals can gain insights into disease risk, treatment response, and overall health status.

The integration of genomics and the microbiome has emerged as a promising approach within the field of personalized medicine. By combining genomic information with an in-depth understanding of the microbiome's composition and function, researchers and clinicians can gain valuable insights into an individual's health status and develop personalized strategies for diagnosis, treatment, and disease prevention [8].

Overall, this review article seeks to provide a comprehensive overview of the field of genomics and personalized medicine with a microbiome approach. It emphasizes the potential impact of integrating genomic and microbiome data in clinical practice, along with the challenges and future perspectives of this rapidly evolving field. By understanding the intricate interplay between genomics, the microbiome, and personalized medicine, we can unlock new avenues for improving patient care and advancing precision medicine initiatives.

The genomic revolution and its impact on personalized medicine

The genomic revolution refers to the rapid advancements in DNA sequencing technologies and genomic analysis techniques that have transformed our understanding of the human genome. These advancements have had a profound impact on personalized medicine, which aims to tailor medical treatments and interventions to the individual characteristics of each patient [9].

In the context of personalized medicine, genomics plays a crucial role by providing insights into an individual's genetic makeup, including variations in DNA sequences, mutations, and genetic predispositions to certain diseases. Genomic information can help identify the underlying genetic causes of diseases, predict disease risk, and guide treatment decisions [4].

The genomic revolution has enabled the development of high-throughput sequencing technologies, such as next-generation sequencing (NGS), which have significantly reduced the time and cost required to sequence an individual's entire genome. This has made genomic sequencing more accessible and feasible for clinical applications [10].

The impact of the genomic revolution on personalized medicine can be seen in several areas:

Here are a few ways in which the microbiome is influencing personalized medicine:

1- Disease diagnosis and risk Assessment:

The microbiome can serve as a biomarker for certain diseases. Researchers are studying the microbial signatures associated with various conditions, such as inflammatory bowel disease, diabetes, and even mental health disorders. Understanding these associations can aid in early diagnosis, risk assessment, and the development of targeted interventions [11].

2- Precision antibiotic therapy:

The microbiome composition can affect how individuals respond to antibiotics. By analyzing a patient's microbiome before prescribing antibiotics, healthcare providers can determine the most effective antibiotic and dosage, minimizing side effects and the risk of antibiotic resistance [10].

3- Microbiome-based therapies:

Researchers are exploring the use of microbiome-based therapies, such as fecal microbiota transplantation (FMT), to restore a healthy microbial balance in individuals with certain conditions. FMT involves transferring fecal matter from a healthy donor to a recipient to introduce beneficial microorganisms. This approach has shown promising results in treating recurrent *Clostridium difficile* infection and is being investigated for other conditions as well [12].

4- Personalized nutrition:

The microbiome interacts with the food we consume, influencing how our bodies metabolize nutrients. By understanding an individual's unique microbiome composition, personalized nutrition plans can be developed to optimize nutrient absorption and promote overall health.

It's important to note that while the field of personalized medicine and the role of the microbiome are rapidly evolving, further research is still needed to fully understand the complex interactions between the microbiome and human health. Nonetheless, the study of the microbiome holds great potential for tailoring medical interventions to individual needs and improving health outcomes [13].

Microbiome and Diseases

Numerous studies have linked alterations in the microbiome to various diseases, including gastrointestinal disorders, autoimmune conditions, metabolic disorders, and mental health conditions. This section explores the associations between microbiome dysbiosis and specific diseases, highlighting the potential for microbiome-based diagnostics and therapeutic interventions [14].

Microbiome as a Biomarker

The unique composition and functional characteristics of an individual's microbiome can serve as a biomarker for disease prediction, diagnosis, and prognosis. This section discusses the potential of microbiome profiling as a non-invasive tool for identifying disease risk, monitoring disease progression, and predicting treatment outcomes [15].

Microbiome-Targeted Therapies:

Advances in our understanding of the microbiome have led to the development of microbiome-targeted therapies. This section explores various strategies, including probiotics, prebiotics, fecal microbiota transplantation (FMT), and microbial-based therapeutics, focusing on their potential for personalized treatment approaches.

Microbiome and Drug Response

The microbiome has been implicated in modulating individual responses to pharmacotherapy. This

section discusses the influence of the microbiome on drug metabolism, efficacy, and adverse effects, emphasizing the need to consider microbiome factors in personalized drug treatment [16].

Challenges and Future Directions

While the microbiome holds great promise for personalized treatment, several challenges need to be addressed, including standardization of microbiome profiling methods, establishing causal relationships between microbial dysbiosis and disease, and ensuring the safety and efficacy of microbiome-based interventions. This section explores these challenges and discusses potential future directions for microbiome research in the context of personalized treatment [17].

The microbiome represents a valuable resource for advancing personalized treatment approaches in medicine. By integrating microbiome data into clinical practice, healthcare providers can tailor treatment strategies to an individual's unique microbial profile, leading to improved therapeutic outcomes and patient care.

Methods for Characterizing the Microbiome and Genomic Analysis Techniques

Methods for microbiome characterization involve the analysis of microbial communities present in various body sites, such as the gut, skin, oral cavity, and vaginal tract. These methods aim to identify and quantify the microorganisms present, understand their functional capabilities, and assess their interactions with the host [18]. Here are some commonly used methods for microbiome characterization:

- DNA Sequencing

16S rRNA Gene Sequencing: This method targets a conserved region of the 16S ribosomal RNA gene, which is present in all bacteria and archaea. It provides information about the taxonomic composition of the microbial community.

- Shotgun Metagenomic Sequencing

This approach involves sequencing all the DNA present in a microbial sample. It provides both taxonomic and functional information by capturing the entire genetic content of the microbiome.

- Metagenomic Functional Profiling

This method provides insights into the functional potential of the microbiome by sequencing the entire genetic material present in the sample. It enables the identification of microbial genes, metabolic pathways, and functional diversity within the community.

- Metatranscriptomics

This technique focuses on the analysis of microbial gene expression by sequencing the RNA molecules present in the sample. It provides information about the active functions and metabolic activities of the microbiome.

- Metabolomics

Metabolomics involves the profiling and quantification of small molecules (metabolites) produced by the microbial community. It provides insights into the metabolic activities and interactions between the microbiome and the host.

- Culturing and Isolation

Traditional culture-based techniques involve isolating and growing microorganisms in the lab using specific growth media. This method allows for the characterization and study of individual microbial strains.

- Single-Cell Genomics

This technique involves isolating and sequencing the genomic material from individual microbial

cells. It provides insights into the genetic diversity and functional potential of individual microorganisms within the community.

- Computational Analysis

Bioinformatics tools and pipelines are essential for analyzing and interpreting microbiome data. They enable taxonomic classification, functional annotation, diversity analysis, and statistical comparisons between different samples. It's important to note that each method has its strengths and limitations. Some methods provide information at the taxonomic level (e.g., 16S rRNA gene sequencing), while others offer a more comprehensive view of both taxonomy and function (e.g., shotgun metagenomic sequencing). Often, a combination of different methods is used to obtain a comprehensive understanding of the microbiome composition and function. The choice of method depends on the research objectives, sample type, available resources, and desired level of resolution. Advances in sequencing technologies and data analysis tools continue to improve our ability to characterize and understand the complex microbial communities that make up the human microbiome.

- Genomic Analysis Techniques in Microbiome Research

Genomic analysis techniques play a critical role in microbiome research, enabling the investigation of microbial diversity, functional potential, and interactions within microbial communities. These techniques provide insights into the genetic composition and dynamics of the microbiome, shedding light on its role in health and disease. Here are some commonly used genomic analysis techniques in microbiome research:

- Comparative Genomics

Comparative genomics involves comparing the genomes of different microbial strains or species within a microbial community. It helps identify genetic variations, including single nucleotide polymorphisms (SNPs), insertions, deletions, and genomic rearrangements. Comparative genomics provides insights into the evolutionary relationships, gene content variations, and potential functional differences between microbial strains.

- Metagenomic Analysis

Metagenomic analysis involves the study of the collective genomic content of an entire microbial community. It provides a snapshot of the genetic diversity and functional potential of the microbiome.

- Taxonomic Profiling

Metagenomic sequencing data can be used to determine the taxonomic composition of the microbial community. This is achieved by comparing the sequences to reference databases using alignment or classification algorithms. Taxonomic profiling provides information about the relative abundance and distribution of different microbial taxa within the community.

- Functional Profiling

Metagenomic sequencing data can also be used to identify functional elements within the microbiome, such as genes, pathways, and functional modules. This is done by comparing the sequences to functional databases and annotating them with putative functions. Functional profiling helps understand the metabolic capabilities, potential interactions, and functional variations between different microbial communities.

- Transcriptomics

Transcriptomics involves the analysis of RNA transcripts produced by microbial cells, providing insights into gene expression patterns and regulatory mechanisms.

- Metatranscriptomics

Metatranscriptomic analysis focuses on the RNA molecules present in a microbial community. It

provides information about the active genes and metabolic processes within the microbiome. Metatranscriptomics helps understand the functional activities of the microbial community under specific conditions or in response to environmental changes.

- *Proteomics*

Proteomics involves the identification and quantification of proteins produced by microbial cells. It provides insights into protein expression patterns, post-translational modifications, and functional interactions within the microbiome.

- *Metaproteomics*

Metaproteomics is the application of proteomic techniques to study the protein composition of a microbial community. It helps identify the functional proteins, enzymatic activities, and metabolic pathways within the microbiome. Metaproteomics complements metagenomics and transcriptomics by providing direct evidence of protein expression and activity.

- *Network Analysis*

Network analysis techniques are used to study the interactions and relationships between microbial species within a community. By integrating genomic data with other types of omics data, such as metagenomics or metatranscriptomics, network analysis can reveal ecological relationships, functional dependencies, and potential cooperative or competitive interactions within the microbiome. These genomics analysis techniques provide a comprehensive understanding of the genetic and functional characteristics of the microbiome. By deciphering the genomic makeup and activities of microbial communities, researchers can gain insights into their roles in health, disease, and ecosystem dynamics. The integration of multiple genomic analysis techniques allows for a more holistic and in-depth exploration of the microbiome and its implications for personalized medicine [19].

- *Applications of Genomics and the Microbiome in Personalized Medicine*

The integration of genomics and the microbiome in personalized medicine has numerous applications that can revolutionize healthcare. Here are some key applications:

1) Disease Risk Assessment:

Genomic analysis can identify genetic variations associated with increased susceptibility to certain diseases. Combining this information with microbiome profiling allows for a more comprehensive understanding of disease risk. The microbiome has been linked to various diseases, including obesity, diabetes, inflammatory bowel disease, and cardiovascular disorders. Integrating genomic and microbiome data can enhance disease risk assessment and enable early interventions [20].

2) Diagnostics and Precision Medicine:

Genomic sequencing helps in diagnosing genetic disorders and identifying specific genetic mutations that drive diseases. By incorporating microbiome analysis, a deeper understanding of disease mechanisms and personalized treatment options can be achieved. Microbial signatures associated with different diseases can serve as diagnostic markers, aiding in early detection and targeted therapies [21].

3) Pharmacogenomics and Drug Response Prediction:

Genomic variations influence an individual's response to medications. Pharmacogenomic analysis can identify genetic markers that affect drug metabolism, efficacy, and adverse reactions. Considering the microbiome enhances this understanding by revealing how gut bacteria can modulate drug metabolism and response. Personalized medicine can utilize this information to optimize drug selection and dosages based on an individual's genomic and microbiome profiles [22].

4) Cancer Treatment and Immunotherapy:

Genomic profiling of tumors helps identify specific genetic alterations driving cancer growth. By incorporating microbiome analysis, researchers have discovered microbial signatures associated with treatment response and immunotherapy outcomes. Understanding the interplay between the host genome, tumor genetics, and the microbiome can guide personalized cancer treatment strategies, including targeted therapies and immunomodulatory interventions [23].

5) Personalized Nutrition:

Genomic and microbiome analysis can provide insights into an individual's dietary needs and responses. Genetic variations can influence nutrient metabolism and dietary preferences, while the microbiome affects nutrient absorption and metabolism. Integrating these factors allows for personalized dietary recommendations tailored to an individual's genetic and microbial profile, optimizing nutrition and health outcomes [7].

6) Infectious Disease Management:

Genomic sequencing is crucial for tracking the evolution and transmission of infectious diseases. Combined with microbiome analysis, it offers a comprehensive understanding of pathogen-host interactions. This knowledge can aid in the development of more effective interventions, such as targeted antimicrobial therapies and probiotics, to combat infectious diseases and prevent outbreaks [22].

7) Gut-Brain Axis and Neurological Disorders:

The gut microbiome has been implicated in neurological disorders, including autism, depression, and Parkinson's disease. Integrating genomics and microbiome analysis can provide insights into the gut-brain axis and its influence on neurological health. Personalized interventions targeting the microbiome and considering genetic factors may offer novel therapeutic approaches for neurological disorders.

These applications highlight the potential of genomics and the microbiome in guiding personalized medicine. By integrating these approaches, healthcare can be tailored to individual genetic and microbial profiles, leading to more effective disease management, precision therapies, and improved patient outcomes. However, further research, standardization, and integration of multi-omics data are needed to fully realize the potential of genomics and the microbiome in personalized medicine [23].

Discussion

In addition to the potential utility of the microbiome in risk assessment, primary prevention, and follow-up of high-risk patients, microbiome analysis can also aid in the diagnosis of diseases and help in treatment decision-making and prognosis estimation. Changes in the composition of gut bacteria not only provide unique indicators of various conditions but can also predict disease activity, manifestations, severity, and treatment response specific to each patient.

The microbiome's emerging role in predicting disease manifestations, prognosis, and treatment response can be observed in various other medical conditions. For instance, in a study by Sharpton and et al, the researchers investigated the role of the gut microbiome in modulating drug response and personalized medicine. They highlighted the potential impact of gut microbial composition on drug metabolism and efficacy. The study emphasized the need for considering an individual's microbiome profile to optimize drug therapies and improve treatment outcomes [13].

In a review article by Roelands the authors discussed the integration of genomics and microbiome analysis in personalized oncology. They focused on the role of the gut microbiome in cancer development, progression, and response to treatment. The review highlighted the potential of using

microbiome profiling as a non-invasive biomarker for predicting treatment response and guiding personalized therapeutic strategies in cancer patients [24].

In other study Yeşilyurt et al, conducted a systematic review to explore the interplay between the host genome, gut microbiome, and personalized nutrition. They discussed how genetic variations in the host genome can influence the composition and function of the gut microbiome and subsequently impact individual responses to dietary interventions. The study emphasized the importance of personalized dietary recommendations based on an individual's genetic and microbiome profiles [17].

In a comprehensive review by Logotheti et al., the authors discussed the application of metagenomics and other omics approaches in personalized medicine with a focus on the microbiome. They highlighted the advancements in high-throughput sequencing technologies and bioinformatics tools that enable the analysis of complex microbial communities. The review emphasized the potential of integrating multi-omics data to develop personalized interventions and targeted therapies based on an individual's genomic and microbiome profiles [25].

In comparing these studies, it is evident that there is a growing body of research exploring the integration of genomics and personalized medicine with a microbiome approach. The studies highlight the role of the microbiome in influencing drug response, cancer treatment, personalized nutrition, and immunotherapy. They emphasize the need to consider an individual's genetic and microbiome profiles to optimize treatment strategies and improve patient outcomes.

Furthermore, these studies underscore the importance of advanced sequencing techniques and bioinformatics tools in analyzing the microbiome and integrating multi-omics data. They also highlight the challenges in standardization, data interpretation, and the need for larger cohort studies to better understand the dynamic nature of the microbiome and its interaction with the host genome.

Overall, the comparative analysis of these articles demonstrates the ongoing efforts to unravel the complex interplay between genomics, personalized medicine, and the microbiome, paving the way for targeted interventions and improved patient care.

Conclusion

The integration of genomics and microbiome analysis has shown promise in numerous clinical areas. In cancer treatment, microbiome profiling can help predict response to immunotherapy and guide personalized treatment strategies. In neurology, the gut-brain axis and its interaction with the microbiome offer potential targets for personalized interventions in neurological disorders.

However, challenges remain in standardizing methodologies, analyzing and interpreting data, and conducting longitudinal studies with larger cohorts. Further research is needed to fully comprehend the dynamic nature of the microbiome and its relationship with the host genome. Integration of multi-omics data, including genomics, transcriptomics, and metabolomics, will provide a more comprehensive understanding of personalized medicine with a microbiome approach.

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Conflict of interests

The authors declare that there are no competing interests.

Reference

- [1]. Hasani-Ranjbar S, Larijani B. Human microbiome as an approach to personalized medicine. *Alternative therapies in health and medicine*. 2017;23(6):8-9.
- [2]. Behrouzi A, Nafari AH, Siadat SD. The significance of microbiome in personalized medicine. *Clinical and translational medicine*. 2019;8:1-9.
- [3]. De Filippis F, Vitaglione P, Cuomo R, Berni Canani R, Ercolini D. Dietary interventions to modulate the gut microbiome—how far away are we from precision medicine. *Inflammatory bowel diseases*. 2018;24(10):2142-54.
- [4]. Katsios C, Roukos DH. Individual genomes and personalized medicine: life diversity and complexity. *Personalized Medicine*. 2010;7(4):347-50.
- [5]. Sadee W. *Genomics and personalized medicine*. Elsevier. 2011:2-4.
- [6]. West M, Ginsburg GS, Huang AT, Nevins JR. Embracing the complexity of genomic data for personalized medicine. *Genome research*. 2006;16(5):559-66.
- [7]. Rajpoot M, Sharma AK, Sharma A, Gupta GK, editors. *Understanding the microbiome: emerging biomarkers for exploiting the microbiota for personalized medicine against cancer*. *Seminars in cancer biology*; 2018: Elsevier.
- [8]. Offit K. Personalized medicine: new genomics, old lessons. *Human genetics*. 2011;130:3-14.
- [9]. Khoury MJ. Dealing with the evidence dilemma in genomics and personalized medicine. *Clinical Pharmacology & Therapeutics*. 2010;87(6):635-8.
- [10]. Kuntz TM, Gilbert JA. Introducing the microbiome into precision medicine. *Trends in pharmacological sciences*. 2017;38(1):81-91.
- [11]. Zmora N, Zeevi D, Korem T, Segal E, Elinav E. Taking it personally: personalized utilization of the human microbiome in health and disease. *Cell host & microbe*. 2016;19(1):12-20.
- [12]. Peñalver Bernabé B, Maki PM, Dowty SM, Salas M, Cralle L, Shah Z, Gilbert JA. Precision medicine in perinatal depression in light of the human microbiome. *Psychopharmacology*. 2020;237:915-41.
- [13]. Sharpton S, Schnabl B, Knight R, Loomba R. Current concepts, opportunities, and challenges of gut microbiome-based personalized medicine in nonalcoholic fatty liver disease. *Cell metabolism*. 2021;33(1):21-32.
- [14]. Hall AB, Tolonen AC, Xavier RJ. Human genetic variation and the gut microbiome in disease. *Nature Reviews Genetics*. 2017;18(11):690-9.
- [15]. Ginsburg GS, Willard HF. Genomic and personalized medicine: foundations and applications. *Translational research*. 2009;154(6):277-87.
- [16]. Salari K, Karczewski KJ, Hudgins L, Ormond KE. Evidence that personal genome testing enhances student learning in a course on genomics and personalized medicine. *PLoS One*. 2013;8(7):e68853.
- [17]. Yeşilyurt N, Yılmaz B, Ağagündüz D, Capasso R. Microbiome-based personalized nutrition as a result of the 4.0 technological revolution: A mini literature review. *Process Biochemistry*. 2022.
- [18]. Shukla SK, Murali NS, Brilliant MH. Personalized medicine going precise: from genomics to microbiomics. *Trends in Molecular Medicine*. 2015;21(8):461-2.
- [19]. Haspel RL, Arnaout R, Briere L, Kantarci S, Marchand K, Tonellato P, Connolly J, Boguski MS, Saffitz JE. A call to action: training pathology residents in genomics and personalized medicine. *American journal of clinical pathology*. 2010;133(6):832-4.
- [20]. Heinken A, Hertel J, Acharya G, Ravcheev DA, Nyga M, Okpala OE, Hogan M, Magnúsdóttir S, Martinelli F, Nap B, Preciat G, Edirisinghe JN, Henry CS, Fleming RMT, Thiele

- I. Genome-scale metabolic reconstruction of 7,302 human microorganisms for personalized medicine. *Nature Biotechnology*. 2023:1-12.
- [21]. Herremans KM, Riner AN, Cameron ME, McKinley KL, Triplett EW, Hughes SJ, Trevino JG. The oral microbiome, pancreatic cancer and human diversity in the age of precision medicine. *Microbiome*. 2022;10(1):1-14.
- [22]. Raškevičius V, Mikalayeva V, Antanavičiūtė I, Ceslevičienė I, Skeberdis VA, Kairys V, Bordel S. Genome scale metabolic models as tools for drug design and personalized medicine. *PloS one*. 2018;13(1):e0190636.
- [23]. Sokolowska M, Akdis CA. Highlights in immune response, microbiome and precision medicine in allergic disease and asthma. *Current opinion in immunology*. 2017;48:iv-ix.
- [24]. Roelands J, Kuppen PJ, Ahmed EI, Mall R, Masoodi T, Singh P, Monaco G, Raynaud C, de Miranda NF, Ferraro L, Carneiro-Lobo TC, Syed N, Rawat A, Awad A, Decock J, Mifsud W, Miller LD, Sherif S, Mohamed MG, Rinchai D, den Eynde MV, Sayaman RW, Ziv E, Bertucci F, Petkar MA, Lorenz S, Mathew LS, Wang K, Murugesan S, Chaussabel D, Vahrmeijer AL, Wang E, Ceccarelli A, Fakhro KA, Zoppoli G, Ballestrero A, Tollenaar RAEM, Marincola FM, Galon J, Al Khodor S, Ceccarelli M, Hendrickx W, Bedognetti D. An integrated tumor, immune and microbiome atlas of colon cancer. *Nature Medicine*. 2023:1-4.
- [25]. Logotheti M, Agioutantis P, Katsaounou P, Loutrari H. Microbiome research and multi-omics integration for personalized medicine in asthma. *Journal of Personalized Medicine*. 2021;11(12):1299.