ANNUAL REVIEWS

Annual Review of Food Science and Technology

Predicting Personalized Responses to Dietary Fiber Interventions: Opportunities for Modulation of the Gut Microbiome to Improve Health

Car Reen Kok,[1,2] Devin Rose,[2,3] and Robert Hutkins[2,3]

[1]Complex Biosystems, University of Nebraska, Lincoln, Nebraska, USA

[2]Nebraska Food for Health Center, University of Nebraska, Lincoln, Nebraska, USA

[3]Department of Food Science and Technology, University of Nebraska, Lincoln, Nebraska, USA; email: rhutkins1@unl.edu

Annu. Rev. Food Sci. Technol. 2023. 14:157–82

First published as a Review in Advance on November 29, 2022

The *Annual Review of Food Science and Technology* is online at food.annualreviews.org

https://doi.org/10.1146/annurev-food-060721-015516

Keywords

prebiotics, gut microbiome, precision nutrition, CAZyme, dietary fiber

Abstract

Inadequate dietary fiber consumption has become common across industrialized nations, accompanied by changes in gut microbial composition and a dramatic increase in chronic metabolic diseases. The human gut microbiome harbors genes that are required for the digestion of fiber, resulting in the production of end products that mediate gastrointestinal and systemic benefits to the host. Thus, the use of fiber interventions has attracted increasing interest as a strategy to modulate the gut microbiome and improve human health. However, considerable interindividual differences in gut microbial composition have resulted in variable responses toward fiber interventions. This variability has led to observed nonresponder individuals and highlights the need for personalized approaches to effectively redirect the gut ecosystem. In this review, we summarize strategies used to address the responder and nonresponder phenomenon in dietary fiber interventions and propose a targeted approach to identify predictive features based on knowledge of fiber metabolism and machine learning approaches.

INTRODUCTION

The human gut microbiome is home to a diverse community of microbes, forming a dynamic and complex ecosystem whose composition has profound effects on host health and well-being (Fan & Pedersen 2020). In the past two decades, numerous studies have demonstrated the important role of diet in shaping the structure of the gut microbiome (David et al. 2015, Healey et al. 2018, A.J. Johnson et al. 2019). Consumption of dietary fiber in particular is a major factor influencing microbiome composition (Gill et al. 2020). Commensurate with modifying the gut microbiota, increased fiber consumption is also associated with an improvement in overall metabolic health as well as reduced risks of obesity, type 2 diabetes, immune diseases, cardiovascular disease, cancer, and colorectal diseases (Barber et al. 2020, X. Liu et al. 2021, So et al. 2021). Low fiber consumption, in contrast, also has important consequences for the gut microbiota. Studies comparing gut metagenomes of rural and urbanized populations (De Filippo et al. 2017, Segata 2015) have linked so-called Western diets to the depletion of gut microbial diversity.

Despite these reports, fiber consumption in the USA and other industrialized countries remains consistently well below recommended dietary guidelines. For example, in contrast to the recommended dietary fiber intake of 25 and 38 g/day, median consumption is only 14.8 and 17.7 g/day for adult women and men, respectively (Inst. Med. 2005, USDA Agric. Res. Serv. 2021). Moreover, fewer than 6% of women and 3% of men meet recommended intakes (USDA Agric. Res. Serv. 2021). Consumption of fiber is also below recommended levels in the European Union and China, where average dietary fiber intake is 21.8 (Deschasaux et al. 2018) and 9.7 g/day (Yu et al. 2020), respectively.

Several mechanistic studies have demonstrated how fiber-rich diets affect the gut microbiome, both compositionally and functionally (Kundi et al. 2021, Tanes et al. 2021). Collectively, these observations suggest that the benefits of fiber consumption for the host are likely mediated by specific microbial groups. These findings have stimulated interest in utilizing various dietary fibers, including prebiotic fibers, as interventions to target growth and enrichment of specific microbes that produce health-associated metabolites. However, several studies have shown that, while effective, such interventions often result in observed changes in the microbiota and beneficial health responses in only a subset of individuals (Kovatcheva-Datchary et al. 2015, Nguyen et al. 2020). In other words, there appear to be fiber nonresponders whose microbiota is unaffected by the intervention and who do not exhibit a targeted response. This result is likely attributable to the complexity and individuality of the gut microbiome, as well as the absence of keystone taxa or functional genes (Maldonado-Gómez et al. 2016, Ze et al. 2012). These findings suggest the need for personalized interventions, either at the individual level or for defined populations. The main challenge for implementing such an approach, however, is to identify, a priori, responders and nonresponders.

Accordingly, the ideal approach to development of personalized nutrition would be to rely on evidence-based predictions of how an individual will respond to a given intervention. Such predictions would require a substantial understanding of the complex interactions within the gut microbial ecosystem, which has recently become possible due to advances in next-generation sequencing technologies, computational tools, and integration of multiomics approaches (Wang et al. 2019). Indeed, interest in using the gut microbiome as a tool for precision nutrition and to address differential responses is evident from the increase in recent publications on this topic (Delzenne & Rodriguez 2022, Hughes et al. 2019b, Gibbons et al. 2022, Johnson et al. 2020, Ojima et al. 2022, Schupack et al. 2022). In this review, we describe the personalized nature of the human gut microbiome and individualized responses toward dietary interventions. We also highlight the importance of microbial carbohydrate genes in fiber metabolism and the potential use of these

genes as targets for personalizing fiber interventions alongside current computational approaches used to predict microbiome responses.

FIBER AND THE GUT MICROBIOME

Dietary fibers are generally defined as polysaccharides and lignin that are resistant to enzymatic digestion in the gastrointestinal tract. They include insoluble components of the plant cell wall, such as cellulose and hemicellulose, as well as soluble substances, such as pectin, inulin, and guar gum. These fibers are widely available in foods such as legumes, nuts, cereals, fruits, and vegetables; the major diet-derived polysaccharides are starch, pectin, arabinoxylan, and cellulose. The health-promoting properties of dietary fiber have historically been a topic of interest in nutrition and biomedicine, leading to the dietary fiber hypothesis. This hypothesis posits that low-fiber diets increase risks of a wide range of noncommunicable diseases, such as cardiovascular diseases, obesity, and colon cancer (Barber et al. 2020, Cummings & Engineer 2018).

Although not digested or absorbed by the human gastrointestinal tract, dietary fiber is classified as an essential nutrient in the US Dietary Guidelines on the basis of the intake observed to protect against coronary heart disease (Inst. Med. 2005). Furthermore, the US Food and Drug Administration has identified several physiological benefits of dietary fibers, including reducing blood glucose, increasing frequency of bowel movements, increasing mineral absorption in the intestinal tract, and reducing energy intake (FDA 2016). Large-scale epidemiological studies throughout the world continue to describe the inverse relationship between dietary fiber consumption and disease occurrence and mortality (Ferrari et al. 2013, Katagiri et al. 2020, Song & Song 2021).

Many of the observed health promoting effects of fiber are mediated through the microbes that reside in the gut. These benefits have been attributed to the effects of fiber fermentation in the colon that stimulates the growth of favorable bacteria resulting in the production of beneficial metabolites, the reduction of luminal and colonic pH, and the competitive exclusion of pathogenic bacteria (Beukema et al. 2020, Gill et al. 2020). In contrast, Sonnenburg & Sonnenburg (2014) noted the profound impacts of a diet that is low in microbiota-accessible carbohydrates on increased inflammation and immune dysregulation. Using gnotobiotic mice models, several studies have reported the direct effects of fiber-depleted diets either on a single strain of bacteria or on microbial communities (Desai et al. 2016, Schroeder et al. 2018, Sonnenburg et al. 2005). These studies collectively observed an erosion of the colonic mucus barrier resulting from a switch in bacterial glycan-foraging metabolism toward host-derived glycans. This finding emphasizes the importance of fiber in preserving the colonic mucosal layer.

Indeed, the production of beneficial metabolites from fiber requires microbial consortia that express specific genes for complex carbohydrate hydrolysis and metabolism (Bai et al. 2021, Parkar et al. 2021). Unlike the human genome, the human gut microbiome is genetically equipped to produce a wide array of carbohydrate-active enzymes (CAZymes) that are required for the metabolism of fiber substrates (Flint et al. 2012). This diversity aligns with the assortment of dietary fibers that are available in the human diet as well as host-derived glycans that vary in monomer composition, spatial orientation, chemical structure, chain length, linkages, and side chains (Armstrong et al. 2021, Coker et al. 2021, Ye et al. 2022). As the complexity of the substrate increases, the number of substrate-specific microbial carbohydrate genes is expected to increase proportionally as well (Castell-Miller et al. 2016, Kong et al. 2020) (**Figure 1**). For example, simple substrates such as fructans might require the activity of one or two CAZyme families, while a more structurally complex substrate, such as pectin, requires at least seven CAZyme families for complete degradation (Hamaker & Tuncil 2014, Ye et al. 2022). In several gnotobiotic mouse and human studies using pea fiber, orange fiber, and barley bran, Delannoy-Bruno et al. (2021) demonstrated

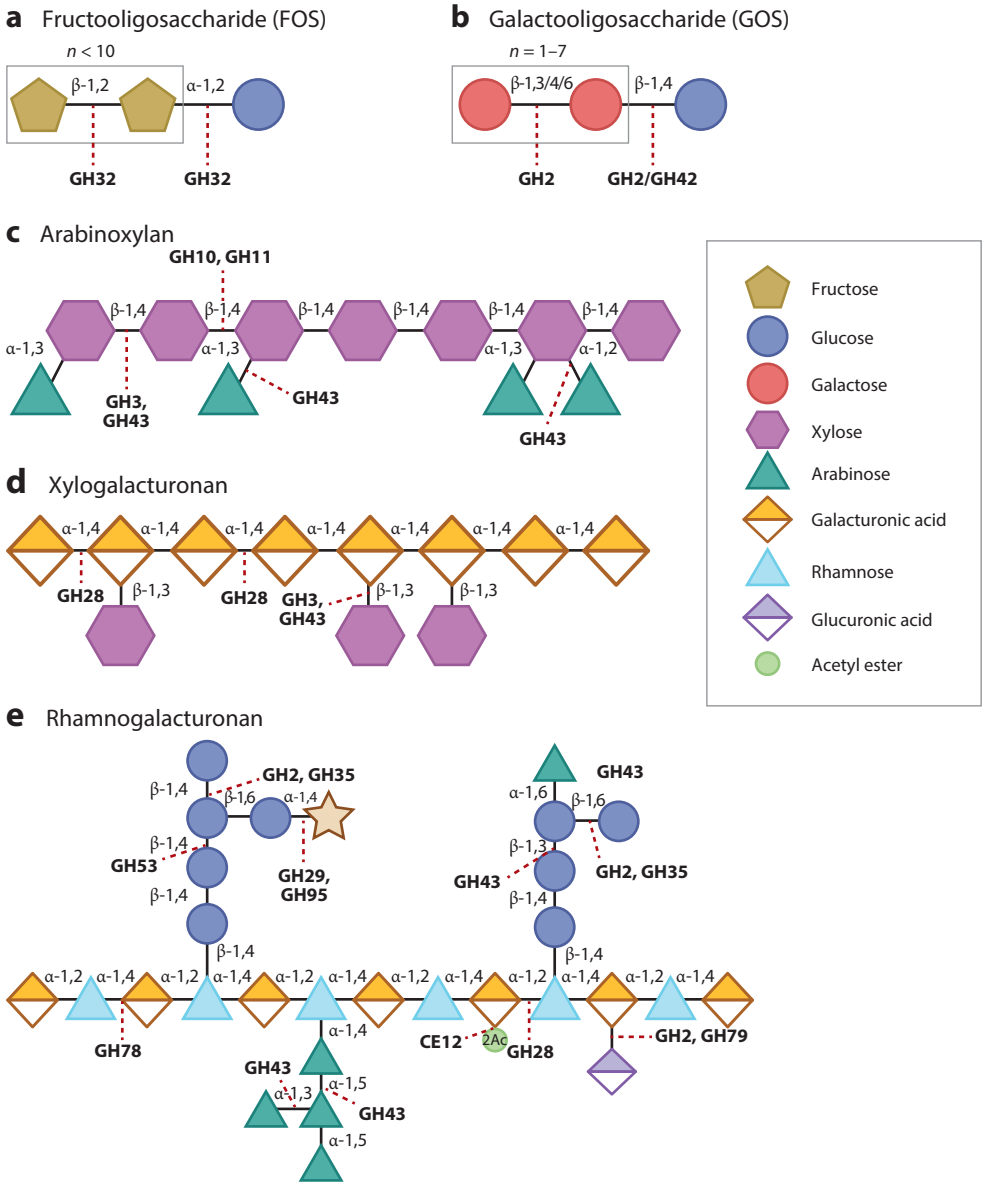

Figure 1

The role of carbohydrate-active enzymes (CAZymes) in fiber metabolism. The gut microbiome encodes for a diverse number of CAZymes that are involved in the degradation of dietary fiber of varying complexities. These include simple oligosaccharides, such as (*a*) fructooligosaccharides and (*b*) galactooligosaccharides, which require few specific CAZymes for degradation, and complex polysaccharides, such as (*c*) arabinoxylan, (*d*) xylogalacturonan, and (*e*) pectin rhamnogalacturonan, which require a diverse array of CAZymes for complete metabolism. The CAZyme families depicted include carbohydrate metabolic genes that carry out specific functions. Figure adapted from images created with BioRender.com.

the enrichment of CAZyme genes that were consistent with the composition of these substrates. In particular, significant enrichment of genes that encode for arabinofuranosidases, β-glucanases, β-xylanases, and polysaccharide lyases was found in both mice and humans fed with arabinan- and galacturonan-rich pea fiber. A follow-up clinical study with pea and orange fiber snacks demonstrated a direct correlation between changes in CAZyme gene abundances, relevant glycosidic linkages, and plasma protein levels (Delannoy-Bruno et al. 2022).

Together, the diversity in fiber composition and the diversity of microbes and microbial genes present in the gut provide both opportunities and challenges for the use of fiber to modulate the microbiome and confer consistent benefits on host health. In the remainder of this review, we highlight the microbiome-dependent effects of fiber interventions in humans, the major mechanisms by which fiber is metabolized by colonic microbes, and strategies for personalized dietary approaches.

PERSONALIZED NATURE OF THE HUMAN GUT MICROBIOME

Initial investigations of the impact of dietary interventions on the human gut microbiome led to the realization that the average outcome of a particular intervention does not reflect responses at the individual level. This discovery has made it difficult to develop dietary interventions that will be effective across individuals in a given population. Moreover, studies that survey the gut microbiome on a global scale have revealed the heterogenetic nature of the gut microbiome across different ethnic and geographical populations (Costea et al. 2017, Gaulke & Sharpton 2018). Likewise, Costea et al. (2017) described the presence of subspecies populations, identified through genomic single-nucleotide variations, that were specific to a geographical location and were dominant within individual hosts. This personalized trait of the gut microbiome is a cumulative product of environment, lifestyle, and genetics and likely contributes to the variability in host responses toward various interventions (Benson et al. 2010, Dong & Gupta 2019, Hitch et al. 2022, Zhernakova et al. 2016).

Diet, in particular, has been explored as one of the dominant factors that shape gut microbial composition (Cotillard et al. 2022, Medawar et al. 2021, Singh et al. 2017). By comparing the fecal microbiomes of individuals who practiced caloric restriction with those who did not, Griffin et al. (2017) demonstrated that dietary habits have a profound effect on shaping the responses of microbial communities toward different dietary interventions. In addition, several studies have reported that genetics plays a limited role in influencing microbiome composition. Through associations of ancestral or genetic similarity data with different measures of gut microbial composition from more than 1,000 healthy individuals, Rothschild et al. (2018) concluded that microbial composition was influenced predominantly by environmental factors, such as diet and drug use, while host genetics was weakly influential. Also, results from the PREDICT 1 study revealed that longitudinal measurements of gut microbiome composition within a subject were considerably more similar than measurements within twin pairs, suggesting high individuality beyond genetic factors (Asnicar et al. 2021). In the same cohort, host genetic variation had weak impacts on postprandial metabolic responses to standardized meals (Berry et al. 2020).

Several studies comparing gut microbial composition across different global populations have revealed insights into the coevolution of the gut microbiome with distinct dietary practices (De Filippo et al. 2010, Martínez et al. 2015, Rampelli et al. 2015, Tamburini et al. 2022). Collectively, these studies observed differences between urban and nonindustrialized lifestyles in taxonomic composition, diversity, or abundance. In a study comparing gut microbial composition of European and African children, investigators observed an enrichment in saccharolytic species in the African population, which was consistent with their polysaccharide-rich diet (De Filippo et al. 2010). Similarly, the gut microbiome of Hadza hunter-gatherers harbored fiber-degrading

species that were abundant in comparison to Italian controls, suggesting an adaptation toward a plant-based diet that was characteristic of their foraging lifestyle (Schnorr et al. 2014).

INDIVIDUALIZED RESPONSES TOWARD DIETARY INTERVENTIONS RESULT IN RESPONDER AND NONRESPONDER PHENOTYPES

While the above observations demonstrate the influence of dietary habits on gut microbial composition, in part by targeting expansion of specific taxa, a growing body of evidence suggests that microbial responses to food are in fact highly personalized. This finding is clearly demonstrated in the PREDICT 1 study, which observed individualized postprandial responses toward standardized test meals across 1,002 individuals (Berry et al. 2020). Similarly, by modeling personalized diet–microbiome interactions for each of their study participants, A.J. Johnson et al. (2019) observed that food–microbe interactions were inconsistent across individuals.

Many other dietary fiber intervention studies have led to the observation of responders and nonresponders in both healthy and unhealthy populations (**Table 1**). In a cohort of obese patients, differential responses in change in body mass index (BMI) were observed after 3 months of inulin supplementation (Rodriguez et al. 2020). Some of the taxonomic features of responders (decrease in BMI) included higher abundance of *Akkermansia* and *Butyricicoccus* and a lower abundance

Table 1 Dietary fiber studies reporting responders and nonresponders based on defined measurable outcomes

Dietary fiber	Cohort health status	Measured response	Responders	Nonresponders	Reference(s)
Inulin	Obese	BMI	25	26	Rodriguez et al. (2020)
Arabinoxylan	Healthy	Propionate concentrations	6	9	Nguyen et al. (2020)
High fiber/whole grain diet	Overweight/obese	Waist circumference and fat mass	15	21	Hjorth et al. (2018)
Increased dietary fiber intake	Healthy	Microbiome stability pre- and postintervention	85	130	Klimenko et al. (2018)
Barley kernel bread	Healthy (BMI normal to slightly overweight)	Blood glucose metabolism	10	10	Kovatcheva-Datchary et al. (2015)
Diet supplemented with resistant starch or nonstarch polysaccharide	Obese	Microbiome stability pre- and postintervention	7	6	Salonen et al. (2014)
Galactooligosaccharide	Healthy	*Bifidobacterium* abundance	9	9	Davis et al. (2010, 2011)
Resistant starch 4	Healthy	*Bifidobacterium* abundance	6	4	Martínez et al. (2010)
Resistant starch 2			5	5	
Biscuits containing partially hydrolyzed guar gum and fructooligosaccharides	Healthy	*Bifidobacterium* abundance	27[a]	4	Tuohy et al. (2001)
Inulin	Healthy	*Bifidobacterium* abundance	20	10	Kolida et al. (2007)

[a]15 subjects had a ≥0.5 log increase, and 12 subjects had a <0.5 log increase.

of *Anaerostipes* at baseline. Likewise, among subjects consuming a barley kernel–based bread (Kovatcheva-Datchary et al. 2015), the same number of subjects ($n = 10$ in each group) could be classified as either responders or nonresponders on the basis of improved glucose metabolism. Responders also exhibited an observed increase in *Prevotella copri* and genes involved in β-glucan degradation. In subsequent mouse experiments, this observation was mechanistically associated with increased glycogen storage in the liver.

Overall, these studies suggest that the gut microbiome is a complex and heterogeneous trait that drives interindividual responses with observed significant differences in community composition pre- and postintervention. Therefore, while it is possible to modulate the gut microbiome through dietary means, broad conclusions obtained from dietary intervention studies are insufficient to address individualized responses. Thus, a more pragmatic approach to improve the treatment efficacy would be to identify, a priori, microbiome-derived biomarkers to predict and classify subjects (**Figure 2**). Furthermore, identification of discriminatory signatures could be used as a basis to convert a nonresponder into a responder through the delivery of probiotics or genetically engineered species that harbor the functional genes that are absent in an individual's microbiome. Indeed, findings across several studies have proposed the use of baseline gut microbiome signatures as possible predictors of responses toward dietary interventions in patients with metabolic syndrome (Jie et al. 2021, Rodriguez et al. 2020, Valdez-Palomares et al. 2021). In the next section, we discuss the types of measurable responses and how discriminatory signatures can be implemented for subject stratification at baseline.

DEFINING RESPONSES TOWARD DIETARY INTERVENTIONS AND STRATEGIES FOR PREINTERVENTION SUBJECT STRATIFICATION

Depending on the objective of a particular study and the characteristics of the study cohort, responses to a dietary intervention can be defined in several ways (**Figure 3**). In many studies, responses are based on taxonomic outcomes, including changes in abundance of a single taxon and shifts in microbial composition or diversity. While informative functional inferences can be made from taxonomic analyses, they are speculative and are not directly relevant to host responses. Nevertheless, this approach is important at initial phases of discovery, when the exact effect of an intervention on the gut microbiome, and subsequently the host, is unknown. Researchers can then hypothesize possible implications of observed compositional shifts and taxonomic associations for host health and design appropriate follow-up studies.

According to numerous reports on the role of *Bifidobacterium* species in fiber metabolism, a notable example of a single taxonomic response is the enrichment of this species toward prebiotic fibers (Probert et al. 2004, Van Den Abbeele et al. 2021, Yoshida et al. 2021). In fact, several studies have defined responders and nonresponders by measuring the abundance of *Bifidobacterium* after supplementation of prebiotic fibers such as galactooligosaccharide (GOS), agave inulin, and human milk oligosaccharide (HMO) (Azcarate-Peril et al. 2017, Elison et al. 2016, Holscher et al. 2015). Davis et al. (2010) observed responders and nonresponders toward GOS supplementation, as only half of the study population ($n = 18$) exhibited significant increases in *Bifidobacterium* in a dose-dependent manner.

Apart from single taxonomic changes, overall shifts in microbial composition, diversity, and stability have also been evaluated as responses. Salonen et al. (2014) tested responsiveness of the gut microbiome in obese individuals toward four sequential, fully controlled diets by using within-subject correlations of microbiome profiles pre- and postintervention. They defined nonresponders as individuals with high microbiome stability and found that they were associated with high microbial diversity. Similarly, in response to a short-term high-fiber dietary intervention,

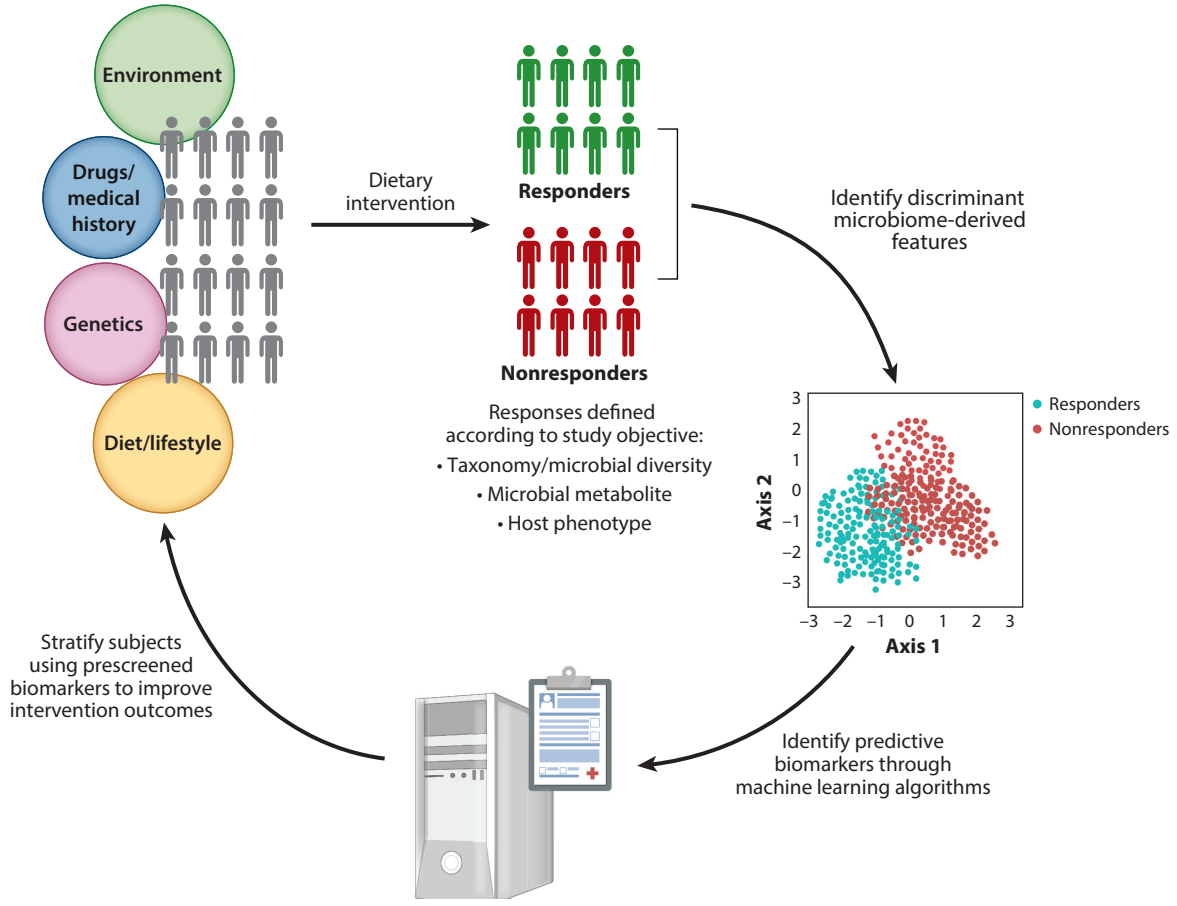

Figure 2

Schematic representation of a conceptual approach to identify predictive microbiome-derived biomarkers that can differentiate between responders and nonresponders toward a particular dietary intervention. The heterogeneous gut microbiome is a result of multiple factors, including environment, drug use, host genetics, and diet or lifestyle choices. Collectively, these factors affect the responsiveness of the gut microbiome toward dietary interventions, resulting in apparent responders and nonresponders. In order to identify underlying dissimilarities between phenotypes, responses need to be rationally defined according to the intervention and the study objective or hypothesis. Through the use of bioinformatics approaches combined with machine learning algorithms, differential biomarkers can be identified and used to predict responses from microbiome data. Other host-associated variables, such as age, sex, and lifestyle habits, can be added to refine predictions. Finally, the resulting predictive model can be used to inform subject stratification and improve the success rate of an intervention. Figure adapted from images created with BioRender.com.

Klimenko et al. (2018) defined responders as individuals who had less stable microbial communities compared with nonresponders. Responders were later discovered to be Bacteroidetes-rich, while nonresponders were Firmicutes-rich at baseline. Several studies have also evaluated the Firmicutes/Bacteroidetes ratio as a response toward different dietary interventions in obese patients, elucidating the role of these species in energy harvest and their impact on obesity (Magne et al. 2020, Parnell & Reimer 2012, Pisanu et al. 2020).

Anthropometric indicators and symptom questionnaires have also been used to evaluate host responses. For example, Jie et al. (2021), Muñoz Pedrogo et al. (2018) and Rodriguez et al. (2020) evaluated responses of obese patients toward lifestyle and dietary interventions by measuring

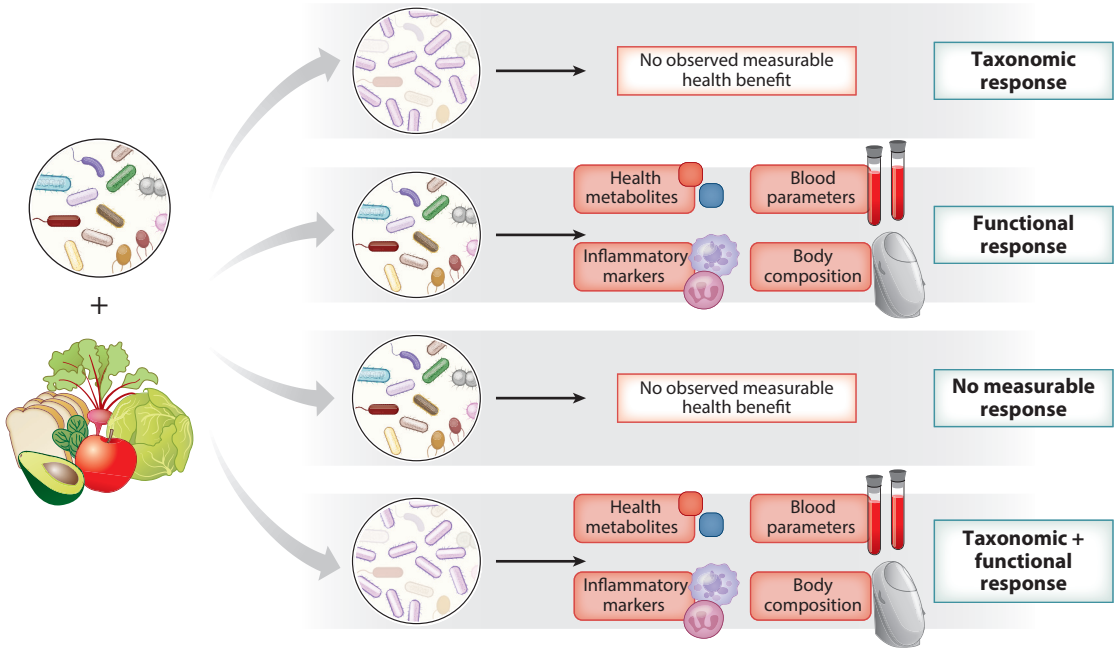

Figure 3

Responses toward dietary interventions. Responses can be taxonomic, functional, or both, depending on the study objectives. A taxonomic response is defined as a shift in microbial composition or abundance, while a functional response includes other measurable readouts, such as metabolite concentration, body composition, and blood parameters, that are associated with host health. A taxonomic response does not necessarily result in a functional response; similarly, a functional response does not always reflect taxonomic shifts. Figure adapted from images created with BioRender.com.

changes in BMI. Similarly, Valdez-Palomares et al. (2021) determined response status of a cohort of patients with irritable bowel syndrome toward a low-FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet according to self-reported severity of symptoms. All four studies reported associations between responder/nonresponder phenotypes and microbiome composition at baseline.

Other parameters used as indicators of host health are targeted health markers such as specific metabolites, inflammatory markers, or blood glucose levels (Korpela et al. 2014, Kovatcheva-Datchary et al. 2015, Ramos-Romero et al. 2021). In three different obese cohorts, Korpela et al. (2014) evaluated host responsiveness by measuring total blood cholesterol, insulin sensitivity, C-reactive protein (an indicator of systemic inflammation), and microbiome stability toward different health-associated dietary interventions. Interestingly, the taxa associated with each of these responses differed depending on the response variable, emphasizing the importance of formulating hypothesis-driven responses to answer specific questions.

Short-chain fatty acids (SCFAs), primarily acetate, propionate, and butyrate, have been widely used as metabolic indicators. These metabolites are a by-product of fermentation in the colon, reflecting community-wide carbohydrate metabolism while accounting for functional redundancy within individual microbiomes (Reichardt et al. 2018). SCFAs act as a primary energy source for colonic cells and have anti-inflammatory and anticarcinogenic properties (Holscher 2017, Wenzel et al. 2020). In addition, multiple prebiotic studies have shown, both in vitro and in vivo, that changes in SCFA responses are personalized and heterogeneous across samples, displaying

unique SCFA profiles that differ depending on the substrate (Gurry et al. 2021, Holmes et al. 2022, Nguyen et al. 2020, Poeker et al. 2018).

The measured responses described above can be used to categorize subjects, typically into two groups—responders and nonresponders—and then to identify discriminatory features of the host or the microbiome at baseline. These features can then be used in follow-up studies to stratify subjects prior to an intervention, improving study outcomes with increased statistical power (Johnson et al. 2020, Leeming et al. 2021, Liu et al. 2020). Proposed strategies for subject stratification include the use of microbiome enterotypes such as *Prevotella*-, *Bacteroides*-, or *Ruminococcus*-dominant enterotypes (Arumugam et al. 2011, Chen et al. 2017). In a fiber intervention study, Christensen et al. (2018) observed that a high-fiber diet had greater efficacy in weight loss for individuals with *Prevotella* enterotypes versus those with *Bacteroides* enterotypes. Similarly, Chen et al. (2017) observed differences in fiber-utilizing capacity across three different fibers, with *Prevotella* enterotypes producing higher SCFA concentrations versus *Bacteroides* enterotypes. However, the use of enterotypes as a general feature is unclear, as the dominance of an enterotype across a population is dependent on other confounding factors such as diet, exercise, and antibiotic use (Mobeen et al. 2018). Additionally, a follow-up study (Sandberg et al. 2019) to the barley kernel bread intervention described above stratified subjects a priori into responders (high *Prevotella*/*Bacteroides* ratio) and nonresponders (low *Prevotella*/*Bacteroides* ratio). However, an improvement in glucose tolerance was independent of baseline abundances of *Prevotella* and *Bacteroides*, although cardiometabolic benefits appeared to be mediated by an expansion in *Prevotella* species. Overall, these findings reflect a challenge in the application of stratification biomarkers that were observed postintervention and were presumed to be predictive.

Another proposed strategy is to classify subjects on the basis of dietary habits. In an inulin intervention study in New Zealand, the dietary habits of participants were first assessed, and then the participants were classified as either high– or low–dietary fiber consumers (Healey et al. 2018). The researchers showed that subjects with a high dietary fiber intake had greater taxonomical responses toward inulin, reflected by an increase in *Bifidobacterium* and *Faecalibacterium* and a decrease in *Coprococcus*, *Dorea*, and *Ruminococcus*. In contrast, subjects with low dietary fiber intake had an increase in only *Bifidobacterium* and appeared to be more resilient.

Functional genes obtained from shotgun metagenomic sequencing can also be used for subject stratification. Using more than 2,000 metagenomes across eight different studies and seven different diseases, Armour et al. (2019) evaluated the potential of functional modules to predict disease states. These investigators concluded that the predictive accuracy was disease dependent. Importantly, the results showed that Crohn's disease and liver cirrhosis had microbiome signatures that were different enough to discern from healthy controls.

In summary, responses toward dietary interventions are variable and should be selected on a rational basis that is relevant to the treatment, the study cohort, and the experimental methodology. Researchers need to understand the effects of a particular dietary intervention prior to selecting a response that can be used to categorize subjects into responders and nonresponders. This is especially important in studies that investigate the role of the gut microbiome in personalized interventions, as the successful identification of underlying biomarkers that differentiate responders and nonresponders is highly dependent on the selected targeted response.

DIETARY FIBER METABOLISM IN THE GUT IS DEPENDENT ON SPECIES THAT ENCODE FOR CARBOHYDRATE-DEGRADING GENES

Increased rates of microbiome-associated pathologies in industrialized populations are associated with changes in microbiome composition and, in particular, depletion of microbial diversity in the

gut (Makki et al. 2018, Segata 2015, Sonnenburg et al. 2016). Prolonged low-fiber consumption, characteristic of a Western diet, has been proposed as a major factor leading to the extinction of bacterial species across generations due to the dependency of these species on complex carbohydrates as carbon and energy sources (Moeller 2017, Sonnenburg et al. 2016). Therefore, most dietary intervention studies have focused on the use of dietary fibers to reestablish a gut microbiota that is protective or beneficial to the host.

Because the human genome encodes for only a limited number of carbohydrate utilization genes, the breakdown of complex carbohydrate substrates in the gut relies heavily on the prevalence of microbial carbohydrate-degrading genes of microbial origin (Bhattacharya et al. 2015, Cantarel et al. 2012, El Kaoutari et al. 2013, Sheridan et al. 2015). These genes include CAZymes that are known to be involved in fiber utilization and fermentation, resulting in the production of desirable metabolic responses (Creswell et al. 2020, Gurry et al. 2018, Ma et al. 2020). CAZymes are classified into families based on their protein sequence similarity and comprise several enzyme classes, including glycoside hydrolases (GHs), glycosyltransferases, polysaccharide lyases (PLs), carbohydrate esterases (CEs), and carbohydrate-binding modules (Lombard et al. 2014). While these enzyme families do not elucidate exact functionality, they provide useful insights into substrate preferences (Flint 2020) and are involved in digestion and utilization of di-, oligo-, and polysaccharides of varying complexities, allowing the gut microbiome to readily switch between different sources of energy.

Many dietary fiber studies have focused on the enrichment of species of *Bifidobacterium* and Lactobacillaceae that have historically been considered beneficial and are known to metabolize a wide range of substrates (Goh & Klaenhammer 2015, Sanders et al. 2018). In particular, the ability of *Bifidobacterium* to utilize a wide repertoire of prebiotic fibers is well established (S. Liu et al. 2021, Soverini et al. 2016). In fact, it is estimated that more than 8% of annotated genes found in genomes of *Bifidobacterium* are dedicated to carbohydrate metabolism (Wang et al. 2020). Examples of prebiotic fiber–associated CAZymes in *Bifidobacterium* include GH43 for arabinoxylan-derived oligosaccharides, GH2 and GH42 for GOS, and GH32 for inulin-type fructans (Ambrogi et al. 2019, Cecchini et al. 2013, Falony et al. 2009, Saito et al. 2020). With improvements in sequencing technologies and computational tools accompanied by the application of culturomics (Lagier et al. 2018), researchers have been able to identify taxa beyond species of *Bifidobacterium* and Lactobacillaceae. These include *Akkermansia*, *Christensenella*, and *Faecalibacterium* species that have since been characterized and associated with various potential health benefits to the host (Chang et al. 2019, O'Toole et al. 2017).

Using mono- and coculture experiments, researchers have begun to discover and describe specific carbohydrate gene machinery in relation to different substrates (Cecchini et al. 2013, Joglekar et al. 2018). For example, studies have shown that an unusually high number of pectin-specific genes encoding for CE and PL enzymes are present in the genome of a highly specialized primary degrader of pectin, *Monoglobus pectinilyticus* (Kim et al. 2019). Moreover, coculture experiments demonstrated the occurrence of cross-feeding reactions and evolved cooperation between gut commensal species that are dependent on their carbohydrate affinities and degradation capabilities (Boger et al. 2018, Rakoff-Nahoum et al. 2016). Boger et al. (2018) experimentally demonstrated that, in the presence of a β-(2,1)-fructan, the expression of an extracellular *Lacticaseibacillus paracasei* exo-inulinase (GH32) increased the availability of fructooligosaccharides for other bacteria species. Additionally, cross-feeding reactions between *Bifidobacterium* and butyrate-producing species such as *Roseburia* and *Anaerostipes* have highlighted the importance of these reactions in the net production of beneficial metabolites (De Vuyst & Leroy 2011, Rivière et al. 2016).

Concurrent with individualized taxonomic profiles described in the previous sections, CAZyme profiles are also heterogeneous across individual microbiomes and are reflective of dietary habits

(Bhattacharya et al. 2015, Rampelli et al. 2015, Soverini et al. 2017). Accordingly, higher CAZyme diversity has been reported in rural and hunter-gatherer populations compared with urban populations (Bhattacharya et al. 2015, Rampelli et al. 2015). Conversely, subsequent comparative analyses have highlighted a greater abundance of nonspecialized GH families (GH43, GH2 and GH3) in industrialized populations compared with preagricultural populations, suggesting a higher diversity of glycans in modern-day diets in parallel with access to a wider variety of foods (Mancabelli et al. 2017). In addition, Bhattacharya et al. (2015) demonstrated that CAZyme profiles of adults are distinct from those of children and infants, reflecting differences in dietary consumption patterns. By contrast, Vangay et al. (2018) observed a loss in microbiome diversity and function, including significant shifts in CAZyme profiles, in subjects upon immigration from Thailand to the USA. Findings included the loss of glycosyl hydrolases that target β-glucan, β-mannan, cellulose, and xyloglucan, indicating the loss of dietary fiber sources commonly found in Southeast Asia. These findings collectively demonstrate that the functionality of the microbiome, including carbohydrate metabolism, reflects dietary practices and exposure to various glycans in the gastrointestinal environment.

BEYOND CAZymes: THE IMPORTANCE OF ACCESSORY GENES FOR CARBOHYDRATE METABOLISM IN THE GUT

CAZymes alone are insufficient for complete degradation and utilization of carbohydrates. Thus, proposed mechanisms for carbohydrate utilization also include the presence of regulatory elements, transporters, and binding proteins that together form carbohydrate gene clusters (Flint et al. 2012). Systems for glycan utilization known as polysaccharide utilization loci (PULs) have been well characterized in species of *Bacteroides* since the discovery of the starch utilization system (*sus*) in *B. thetaiotaomicron* (Anderson & Salyers 1989, Koropatkin et al. 2012). The *sus* system is characterized by the presence of an outer membrane transporter and carbohydrate binding protein adjacent to carbohydrate-degrading genes. More recently, many *sus* homologs have been discovered in species of *Bacteroides*, accounting for the ability of this organism to metabolize a wide range of plant- and host-derived polysaccharides (Ndeh & Gilbert 2018, Wexler & Goodman 2017).

Similarly, the carbohydrate utilization machineries of other gastrointestinal species of Bacillota and Actinomycetota have been explored. These species have adopted different strategies for glycan degradation through the use of various transport systems (Ndeh & Gilbert 2018). For example, Sheridan et al. (2015) reported the presence of gram-positive PULs that encode for polysaccharide-degrading enzymes, oligosaccharide transporters, and transcriptional regulators in strains of Firmicutes. The transport systems that are prevalent in these gram-positive PULs include ATP-binding cassettes (ABCs), major facilitator superfamily transporters, and phosphotransferase system (PTS) transporters, suggesting specialization in carbohydrate metabolism within these species. In contrast, carbohydrate transport systems in species of *Bifidobacterium* (and typically within the Actinomycetota phylum) are characterized mainly by ABC transporters and occasionally by PTSs (Katoh et al. 2020, Koropatkin et al. 2012, Turroni et al. 2012). The diversity in carbohydrate utilization systems described above provides an opportunity for niche differentiation within the gastrointestinal environment. In addition, researchers have successfully identified associations between prebiotic fiber and specific CAZyme-containing gene clusters through gene–trait matching approaches (Fuhren et al. 2020, S. Liu et al. 2021).

Few studies have highlighted the role of specific transporter genes in carbohydrate metabolism despite their physiological importance. Recently, Munoz et al. (2020) showed that expression of a GOS transporter gene was required in a *Bifidobacterium breve* strain for complete uptake and subsequent degradation of specific GOS substrates. *B. breve* UCC2003 was capable of metabolizing

specific GOS molecules through the expression of two genes, a GH2 β-galactosidase (*bgaA*) and a GOS transporter protein (*bgaB*). While knockout mutants of *bgaA* exhibited a reduced growth rate on the GOS substrates, the knockout mutants of the *bgaB* transporter were unable to grow on the substrates, suggesting that the capability for substrate import is essential for carbohydrate metabolism. Duar et al. (2020) also demonstrated the importance of a specific ABC transport system for the utilization of HMO in strains of *Bifidobacterium longum* subsp. *infantis*.

It is now evident that both CAZymes and carbohydrate gene clusters play important roles in glycan degradation. However, it is important to note that successful fiber utilization can occur either through individual microbe–substrate interactions or through cross-feeding reactions in which essential catabolic functions are shared among multiple taxa. Thus, the microbiome may be able to respond to fiber feeding and generate potentially beneficial fermentation end products only if it collectively harbors the required carbohydrate utilization machinery.

SPECIALIZED GLYCAN DEGRADATION IS A STRAIN-SPECIFIC PROPERTY: A TARGET FOR DIETARY FIBER PERSONALIZATION

As described above, it is now well established that dietary fiber metabolism is dependent on the genetic potential of the gut microbiome. This association had led to the prospect of predicting microbiome responsiveness to fiber interventions on the basis of carbohydrate gene profiles. Indeed, recent findings suggest that differences in response status toward fiber interventions are driven by strain-level capabilities of the microbiome in metabolizing different substrates (Cantu-Jungles & Hamaker 2020, Chung et al. 2016). However, the lack of dietary fiber studies on the metagenomic potential of the microbiome has hindered identification of the functional genes that make up these communities.

16S rRNA amplicon sequencing studies have routinely observed changes in the abundance of gut bacterial species in response to dietary intervention (Swanson et al. 2020). Targeting the variable regions of the 16S sequence has permitted accurate taxonomic identification at the genus level or higher (J.S. Johnson et al. 2019). To investigate changes in functionally relevant genes, bioinformaticians have developed tools to infer metabolic functions from taxonomy (Douglas et al. 2020, Mallick et al. 2019). While informative, these predictions are limited to inferences based on reference genomes in databases, resulting in ambiguous or even erroneous annotations in bacteria species with regions of high genome plasticity (Fitzgerald et al. 2018, Vatanen et al. 2019). This is especially true when evaluating carbohydrate utilization genes, as many studies have shown that strains within a genus, or even a species, display preferential utilization for specific carbohydrates (Rivière et al. 2014). This observed genotypic variation within species is driven by gene mutations and horizontal gene-transfer events that are continuous processes within the gut environment and occur as a result of both biotic and abiotic factors (Groussin et al. 2021, Van Rossum et al. 2020).

Numerous studies have demonstrated the strain-specific property of carbohydrate utilization. For example, Falony et al. (2009) demonstrated differences in the metabolism of inulin-type fructans among 18 *Bifidobacterium* strains in vitro. In species of *Bacteroides*, the gene content of a particular fructan utilization locus was shown to determine its overall fructan utilization specificity, with preferential differentiation between β-(2,1) and β-(2,6) fructans (Sonnenburg et al. 2010). Furthermore, Arboleya et al. (2018) demonstrated that differences in the strain-level pangenome within *Bifidobacterium longum* subsp. *longum* resulted in vastly different prebiotic utilization abilities. Another recent pangenome analysis confirmed the plasticity of *B. longum* in genes associated with carbohydrate utilization and its adaptation to different ecological environments (Díaz et al. 2021).

Owing to the availability and decreased cost of deep sequencing technologies, researchers can now begin to investigate microbial communities beyond taxonomic profiling. Specifically, whole

shotgun metagenomic sequencing provides a basis to extrapolate, annotate, and infer function of genes that are present within communities, while metatranscriptomics can identify genes that are actively expressed. In addition, with improvement in binning methods, it is now possible to obtain strain-level resolution from metagenomic data (Quince et al. 2017, 2021).

Using a droplet microfluidics technique, Villa et al. (2020) demonstrated that primary carbohydrate degraders, although taxonomically distinct, were present in all nine subjects. However, large differences in the abundance of these species (up to a 25-fold range) across subjects suggest that both presence and abundance of strains should be considered when determining the glycan-degrading potential of the microbiome and subsequent responses in vivo. Given the unique microbiome composition across individuals, insights into the specialization of carbohydrate-degrading systems provide opportunities to explore the personalization of dietary fiber utilization. One approach, proposed by Cantu-Jungles & Hamaker (2020), is to design structurally unique fibers that can precisely modulate the gut microbiome. These researchers developed and tested a hierarchical dietary model that describes how structurally complex fibers can target autochthonous bacteria species in a specific manner (Cantu-Jungles et al. 2021). In their model, fibers with low specificity, such as fructooligosaccharides, would be expected to create divergent responses among individuals due to the ability of a wide range of bacteria to degrade and metabolize the substrate, coupled with the heterogeneity of microbial composition across individuals. In contrast, fiber with high specificity, such as β-glucans that are degradable by only a handful of bacteria species, would be expected to result in more predictable and consistent shifts across individuals. In a human clinical trial using three different type IV resistant starches, Deehan et al. (2020) demonstrated the ability of minute structural differences to direct the gut microbiome to produce metabolically distinct outputs. This approach, however, requires a comprehensive understanding of fiber structural complexity to elicit the desired responses. In addition, the target species would have to be present at baseline for the intervention to be successful.

An alternative approach is to predict preferential substrate utilization by genotyping relevant carbohydrate genes at baseline prior to administration of the fiber. In a Japanese cohort, Yoshida et al. (2021) demonstrated that the abundance of an ABC substrate binding protein at baseline indicated a bifidogenic response toward lactulose. Interestingly, their results demonstrated that subjects who have a moderate copy number of the gene responded the best toward lactulose supplementation, suggesting lower and upper thresholds by which the treatment will result in a bifidogenic response. Recently, Watanabe et al. (2021) demonstrated that the presence of an extracellular xylanase in human microbiomes indicated a bifidogenic response toward a diet rich in long-chain xylans. This genotyping approach will require thorough profiling of specific genes that are associated with the substrate of interest and is currently limited by functional annotations that are likely nonspecific for lesser-known substrates. Indeed, a combination of both approaches would be ideal, as the former would guarantee high specificity and the latter would confirm the metabolic capability of the microbial community, allowing for well-designed fiber interventions.

FEATURE SELECTION AND MACHINE LEARNING APPROACHES FOR PREDICTING MICROBIOME RESPONSES

The rapid evolution of sequencing technologies and the dramatic increase in omics data generation have made it possible to apply sophisticated techniques to define, predict, and interpret microbiome-associated phenotypes (Hughes et al. 2019a, Iadanza et al. 2020, Zhou & Gallins 2019). Moreover, current interest in advancing precision medicine to address the occurrence of interindividual responses has encouraged the use of predictive algorithms on large data sets. Given the accumulating evidence of association between the gut microbiome and host health, most of

these efforts in predictive modeling have been focused on identifying disease-specific microbiome signatures (Karlsson et al. 2013, Zhou & Gallins 2019).

Recent studies include the use of microbiome-derived data to predict the prognosis of colorectal cancer, pancreatic cancer, and advanced fibrosis in human nonalcoholic fatty liver disease (NAFLD) (Loomba et al. 2017, Nagata et al. 2022, Oh et al. 2020, Sun et al. 2022, Thomas et al. 2019). Using a combination of microbial species information and gene families from more than 969 fecal metagenomes across five studies, Thomas et al. (2019) identified microbial signatures that were predictive for colorectal cancer. Subsequent validation of their models with independent data sets also resulted in high predictive accuracy [random forest classifier; area under the curve (AUC) 0.84], thus demonstrating the reproducibility of their selected biomarkers. From a Japanese cohort, Nagata et al. (2022) identified gut (AUC 0.78) and oral (AUC 0.82) bacterial species that were predictive of pancreatic ductal carcinoma using random forest classifiers. These signatures were also predictive when using gut metagenomes of separate Spanish (AUC 0.75) and German validation cohorts (AUC 0.80).

Apart from predicting specific diseases, large-scale studies have also utilized predictive tools to discriminate between generally healthy and diseased populations (Gupta et al. 2020, Pasolli et al. 2016). For example, in an effort to formulate a predictive measure for disease likelihood, Gupta et al. (2020) identified core microbial species that were associated with healthy microbiomes. They did so by profiling species-level taxonomy for more than 4,000 human stool metagenomes across healthy and diseased populations. By comparing taxonomic profiles between the two populations, these authors formulated a predictive index, referred to as the Gut Microbiome Health Index (GMHI). Interestingly, the authors also discovered that the GMHI was positively correlated with high-density lipoprotein cholesterol, which is a clinically relevant biomarker of cardiovascular health. Oh et al. (2022) also proposed the use of a gut microbiome index to predict health status on the basis of taxonomic markers identified from 5,135 human fecal samples. Moreover, Pasolli et al. (2016) developed a framework to model the features of a healthy microbiome by using 2,424 metagenomes across eight studies and six diseases. Subsequently, the researchers differentiated healthy and disease states through cross-analyses of independent studies. The use of strain-specific markers in these predictive models resulted in higher prediction accuracy compared with species-level abundances.

Studies that combine microbiome sequencing data and additional clinical metadata have also led to improvements in various phenotypic predictions (Berry et al. 2020, Loomba et al. 2017, Mendes-Soares et al. 2019, Zeevi et al. 2015). In an Israeli cohort of 800 individuals, Zeevi et al. (2015) developed a model for the prediction of highly individualized postprandial glycemic responses to food by integrating microbiome data with personal parameters such as dietary habits and physical activity. Using this algorithm, they designed a short-term personalized dietary intervention that led to successful reduction in postmeal glucose. Mendes-Soares et al. (2019) extended this model to a Midwestern cohort with comparable results, and Berry et al. (2020) similarly predicted postprandial responses in a large-scale cohort from the United Kingdom and the USA by using predictive machine learning approaches. Importantly, these models outperformed current standard practices of predicting postprandial responses based solely on caloric or carbohydrate content in food. Finally, in a smaller study with 86 NAFLD patients, Loomba et al. (2017) extracted a set of 40 features, including 37 microbial species, metrics of microbial diversity, age, and BMI, that could distinguish mild/moderate cases of NAFLD from advanced fibrosis (random forest classifier; AUC 0.936). Together, these studies provide robust evidence for the conceptual use of microbiome-derived features, either alone or in combination with other biomarkers, in predicting host responses and phenotypes.

Although many omics-based methods have been adopted to build the predictive models described above, machine learning approaches are especially beneficial for identifying discrete but discernible patterns in groups of interest. Additionally, machine learning models can be recursively improved with the addition of new data. Accordingly, Vangay et al. (2019) compiled a microbiome learning repository consisting of curated classification and regression tasks to promote the development of machine learning methods among microbiome researchers and algorithm developers. Han & Ye (2019) have also curated a repository of microbial marker genes gathered from publicly available data sets for the purpose of creating microbiome-based predictions. Similarly, Carrieri et al. (2019) and Pasolli et al. (2016) described machine learning workflows specifically for predicting phenotypes from metagenomic data. Recently, Topçuoğlu et al. (2020) proposed a machine learning framework to increase reproducibility and model interpretability in microbiome research.

Generally, machine learning strategies are classified as either supervised or unsupervised. Unsupervised methods are used to explore hidden patterns and underlying data structures in a given data set without predefined traits (Namkung 2020, Zhou & Gallins 2019). In contrast, supervised methods are used to build models that can recognize relationships between a set of features and their associated outcomes. Therefore, supervised machine learning methods are commonly used to predict microbiome host traits, as the data can be prelabeled according to phenotypic traits and traits can then be predicted from a given set of features. Recently, supervised machine learning algorithms, such as regression models, support vector machines, random forest classifiers, or a combination of two or more approaches, have been implemented in host–microbiome phenotyping (Hughes et al. 2019a, Topçuoğlu et al. 2020, Zhou & Gallins 2019). However, prior to feeding data into machine learning algorithms, researchers commonly apply feature selection, which is the selection of a reduced subset of discriminative features, to reduce data dimensionality (Bang et al. 2019, Qu et al. 2019). By eliminating redundant features and instead capturing features that reflect true biological variances, a model's performance can be greatly improved. Examples of feature selection methods commonly used for biological data include recursive feature elimination, linear discriminant analysis, and principal component analysis (Kavitha et al. 2018, Octaria et al. 2020, Zhou & Gallins 2019).

Currently, the use of machine learning models to predict responses in the context of dietary fiber interventions is limited. Instead, most microbiome predictive models focus on discriminating between healthy and disease populations. However, the methodologies used in the studies described above can be readily incorporated into predicting dietary fiber responses. While it is tempting to include large quantities of data when training predictive models, it is also important to consider the functional relevance of the selected features in the context of the particular treatment. Likewise, the practicality and feasibility of using a large number of targeted features in a clinical setting must also be considered. In addition to microbiome-derived features, incorporation of host metadata and dietary intake data into predictive models (Ghaffari et al. 2022) would be highly beneficial for personalizing preclinical response predictions and for subsequent subject stratification.

CONCLUSIONS

The use of microbiome data as a complementary noninvasive diagnostic tool in clinical care is now a reality. However, the prevalence of interindividual differences in microbiome composition and unique host responses toward interventions are major challenges for using these approaches in personalized nutrition and precision medicine. Still, as more phenotype-associated biomarkers are identified from the microbiome, researchers will soon be able to genotype baseline samples, predict responses, and stratify subjects prior to assigning treatments. In this review, we have

described how the heterogeneity of the microbiome, both taxonomically and functionally, drives individualized responses across various interventions. In addition, we have provided evidence on the specialization of genes associated with carbohydrate metabolism in the fermentation of dietary fibers and emphasized the potential use of these genes in predicting responses. To that effect, continued discoveries of the mechanisms involved in the degradative processes of fiber in the gut will be highly informative in establishing specific enzyme–substrate interactions. Nonetheless, translation of microbiome research into practical applications by clinicians remains a formidable challenge. As discussed by several investigators (Harvie et al. 2017, Lockwood & Green 2020), there is a need to educate clinicians on the potential of using microbiome-derived data in clinical care settings that can be applied toward developing personalized recommendations that are realistic and relevant to patients. Therefore, long-term efforts will be needed to consolidate findings across fields of nutrition, dietetics, food science, genetics, and epigenetics to gain comprehensive insights into the integration of holistic approaches to patient care. Moreover, collaborative efforts across these different fields will enhance data collection and experimental protocols, ensuring standardization, practicality, relevance, and generalizability of study outcomes toward the overall goal of improving human health and wellness.

DISCLOSURE STATEMENT

R.H. has received grants and honoraria from food and ingredient companies and is a founder of Synbiotic Health.

ACKNOWLEDGMENTS

We thank Dr. Jennifer Auchtung and Dr. Jacques Izard from the Nebraska Food for Health Center for preliminary review of this article.

LITERATURE CITED

Ambrogi V, Bottacini F, O'Sullivan J, O'Connell-Motherway M, Linqiu C, et al. 2019. Characterization of GH2 and GH42 β-galactosidases derived from bifidobacterial infant isolates. *AMB Express* 9:9

Anderson KL, Salyers AA. 1989. Biochemical evidence that starch breakdown by *Bacteroides thetaiotaomicron* involves outer membrane starch-binding sites and periplasmic starch-degrading enzymes. *J. Bacteriol.* 171:3192–98

Arboleya S, Bottacini F, O'Connell-Motherway M, Ryan CA, Ross RP, et al. 2018. Gene–trait matching across the *Bifidobacterium longum* pan-genome reveals considerable diversity in carbohydrate catabolism among human infant strains. *BMC Genom.* 19:33

Armour CR, Nayfach S, Pollard KS, Sharpton TJ. 2019. A metagenomic meta-analysis reveals functional signatures of health and disease in the human gut microbiome. *mSystems* 4:e00332

Armstrong H, Mander I, Zhang Z, Armstrong D, Wine E. 2021. Not all fibers are born equal: variable response to dietary fiber subtypes in IBD. *Front. Pediatr.* 8:924

Arumugam M, Raes J, Pelletier E, Le Paslier D, Yamada T, et al. 2011. Enterotypes of the human gut microbiome. *Nature* 473:175–80

Asnicar F, Berry SE, Valdes AM, Nguyen LH, Piccinno G, et al. 2021. Microbiome connections with host metabolism and habitual diet from 1,098 deeply phenotyped individuals. *Nat. Med.* 27:321–32

Azcarate-Peril MA, Ritter AJ, Savaiano D, Monteagudo-Mera A, Anderson C, et al. 2017. Impact of short-chain galactooligosaccharides on the gut microbiome of lactose-intolerant individuals. *PNAS* 114:E367–75

Bai J, Li Y, Li T, Zhang W, Fan M, et al. 2021. Comparison of different soluble dietary fibers during the in vitro fermentation process. *J. Agric. Food Chem.* 69:7446–57

Bang S, Yoo DA, Kim SJ, Jhang S, Cho S, Kim H. 2019. Establishment and evaluation of prediction model for multiple disease classification based on gut microbial data. *Sci. Rep.* 9:10189

Barber TM, Kabisch S, Pfeiffer AFH, Weickert MO. 2020. The health benefits of dietary fibre. *Nutrients* 12:3209

Benson AK, Kelly SA, Legge R, Ma F, Low SJ, et al. 2010. Individuality in gut microbiota composition is a complex polygenic trait shaped by multiple environmental and host genetic factors. *PNAS* 107:18933–38

Berry SE, Valdes AM, Drew DA, Asnicar F, Mazidi M, et al. 2020. Human postprandial responses to food and potential for precision nutrition. *Nat. Med.* 26:964–73

Beukema M, Faas MM, de Vos P. 2020. The effects of different dietary fiber pectin structures on the gastrointestinal immune barrier: impact via gut microbiota and direct effects on immune cells. *Exp. Mol. Med.* 52:1364–76

Bhattacharya T, Ghosh TS, Mande SS. 2015. Global profiling of carbohydrate active enzymes in human gut microbiome. *PLOS ONE* 10:e0142038

Boger MCL, van Bueren AL, Dijkhuizen L. 2018. Cross-feeding among probiotic bacterial strains on prebiotic inulin involves the extracellular exo-inulinase of *Lactobacillus paracasei* strain W20. *Appl. Environ. Microbiol.* 84:e01539

Cantarel BL, Lombard V, Henrissat B. 2012. Complex carbohydrate utilization by the healthy human microbiome. *PLOS ONE* 7:e28742

Cantu-Jungles TM, Bulut N, Chambry E, Ruthes A, Iacomini M, et al. 2021. Dietary fiber hierarchical specificity: the missing link for predictable and strong shifts in gut bacterial communities. *mBio* 12:e01028

Cantu-Jungles TM, Hamaker BR. 2020. New view on dietary fiber selection for predictable shifts in gut microbiota. *mBio* 11:e02179

Carrieri AP, Rowe WPM, Winn M, Pyzer-Knapp EO. 2019. A fast machine learning workflow for rapid phenotype prediction from whole shotgun metagenomes. In *Proceedings of the 33rd AAAI Conference on Artificial Intelligence*, pp. 9434–39. Palo Alto, CA: AAAI

Castell-Miller CV, Gutierrez-Gonzalez JJ, Tu ZJ, Bushley KE, Hainaut M, et al. 2016. Genome assembly of the fungus *Cochliobolus miyabeanus*, and transcriptome analysis during early stages of infection on American wildrice (*Zizania palustris* L.). *PLOS ONE* 11:e0154122

Cecchini DA, Laville E, Laguerre S, Robe P, Leclerc M, et al. 2013. Functional metagenomics reveals novel pathways of prebiotic breakdown by human gut bacteria. *PLOS ONE* 8:e72766

Chang CJ, Lin TL, Tsai YL, Wu TR, Lai WF, et al. 2019. Next generation probiotics in disease amelioration. *J. Food Drug Anal.* 27:615–22

Chen T, Long W, Zhang C, Liu S, Zhao L, Hamaker BR. 2017. Fiber-utilizing capacity varies in *Prevotella*- versus *Bacteroides*-dominated gut microbiota. *Sci. Rep.* 7:2594

Christensen L, Roager HM, Astrup A, Hjorth MF. 2018. Microbial enterotypes in personalized nutrition and obesity management. *Am. J. Clin. Nutr.* 108:645–51

Chung WSF, Walker AW, Louis P, Parkhill J, Vermeiren J, et al. 2016. Modulation of the human gut microbiota by dietary fibres occurs at the species level. *BMC Biol.* 14:3

Coker JK, Moyne O, Rodionov DA, Zengler K. 2021. Carbohydrates great and small, from dietary fiber to sialic acids: how glycans influence the gut microbiome and affect human health. *Gut Microbes* 13:e1869502

Costea PI, Coelho LP, Sunagawa S, Munch R, Huerta-Cepas J, et al. 2017. Subspecies in the global human gut microbiome. *Mol. Syst. Biol.* 13:960

Cotillard A, Cartier-Meheust A, Litwin NS, Chaumont S, Saccareau M, et al. 2022. A posteriori dietary patterns better explain variations of the gut microbiome than individual markers in the American Gut Project. *Am. J. Clin. Nutr.* 115:432–43

Creswell R, Tan J, Leff JW, Brooks B, Mahowald MA, et al. 2020. High-resolution temporal profiling of the human gut microbiome reveals consistent and cascading alterations in response to dietary glycans. *Genome Med.* 12:59

Cummings JH, Engineer A. 2018. Denis Burkitt and the origins of the dietary fibre hypothesis. *Nutr. Res. Rev.* 31:1–15

David LA, Materna AC, Friedman J, Campos-Baptista MI, Blackburn MC, et al. 2015. Host lifestyle affects human microbiota on daily timescales. *Genome Biol.* 15:R89

Davis L, Martínez I, Walter J, Goin C, Hutkins RW. 2011. Barcoded pyrosequencing reveals that consumption of galactooligosaccharides results in a highly specific bifidogenic response in humans. *PLOS ONE* 6:e25200

Davis L, Martínez I, Walter J, Hutkins R. 2010. A dose dependent impact of prebiotic galactooligosaccharides on the intestinal microbiota of healthy adults. *Int. J. Food Microbiol.* 144:285–92

De Filippo C, Cavalieri D, Di Paola M, Ramazzotti M, Poullet JB, et al. 2010. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. *PNAS* 107:14691–96

De Filippo C, Di Paola M, Ramazzotti M, Albanese D, Pieraccini G, et al. 2017. Diet, environments, and gut microbiota: a preliminary investigation in children living in rural and urban Burkina Faso and Italy. *Front. Microbiol.* 8:1979

De Vuyst L, Leroy F. 2011. Cross-feeding between bifidobacteria and butyrate-producing colon bacteria explains bifdobacterial competitiveness, butyrate production, and gas production. *Int. J. Food Microbiol.* 149:73–80

Deehan EC, Yang C, Perez-Muñoz ME, Nguyen NK, Cheng CC, et al. 2020. Precision microbiome modulation with discrete dietary fiber structures directs short-chain fatty acid production. *Cell Host Microbe* 27:389–404.e6

Delannoy-Bruno O, Desai C, Castillo JJ, Couture G, Barve RA, et al. 2022. An approach for evaluating the effects of dietary fiber polysaccharides on the human gut microbiome and plasma proteome. *PNAS* 119:e2123411119

Delannoy-Bruno O, Desai C, Raman AS, Chen RY, Hibberd MC, et al. 2021. Evaluating microbiome-directed fibre snacks in gnotobiotic mice and humans. *Nature* 595:91–95

Delzenne NM, Rodriguez J. 2022. Nutrition and microbiome. In *Handbook of Experimental Pharmacology: From Obesity to Diabetes*, ed. J Eckel, K Clément, pp. 57–73. Berlin: Springer

Desai MS, Seekatz AM, Koropatkin NM, Kamada N, Hickey CA, et al. 2016. A dietary fiber–deprived gut microbiota degrades the colonic mucus barrier and enhances pathogen susceptibility. *Cell* 167:1339–53.e21

Deschasaux M, Huybrechts I, Murphy N, Julia C, Hercberg S, et al. 2018. Nutritional quality of food as represented by the FSAm-NPS nutrient profiling system underlying the Nutri-Score label and cancer risk in Europe: results from the EPIC prospective cohort study. *PLOS Med.* 15:e1002651

Díaz R, Torres-Miranda A, Orellana G, Garrido D. 2021. Comparative genomic analysis of novel *Bifidobacterium longum* subsp. *longum* strains reveals functional divergence in the human gut microbiota. *Microorganisms* 9:1906

Dong TS, Gupta A. 2019. Influence of early life, diet, and the environment on the microbiome. *Clin. Gastroenterol. Hepatol.* 17:231–42

Douglas GM, Maffei VJ, Zaneveld JR, Yurgel SN, Brown JR, et al. 2020. PICRUSt2 for prediction of metagenome functions. *Nat. Biotechnol.* 38:685–88

Duar RM, Casaburi G, Mitchell RD, Scofield LNC, Ramirez CAO, et al. 2020. Comparative genome analysis of *Bifidobacterium longum* subsp. *infantis* strains reveals variation in human milk oligosaccharide utilization genes among commercial probiotics. *Nutrients* 12:3247

El Kaoutari A, Armougom F, Gordon JI, Raoult D, Henrissat B. 2013. The abundance and variety of carbohydrate-active enzymes in the human gut microbiota. *Nat. Rev. Microbiol.* 11:497–504

Elison E, Vigsnaes LK, Krogsgaard LR, Rasmussen J, Sørensen N, et al. 2016. Oral supplementation of healthy adults with 2′-*O*-fucosyllactose and lacto-*N*-neotetraose is well tolerated and shifts the intestinal microbiota. *Br. J. Nutr.* 116:1356–68

Falony G, Lazidou K, Verschaeren A, Weckx S, Maes D, De Vuyst L. 2009. In vitro kinetic analysis of fermentation of prebiotic inulin-type fructans by *Bifidobacterium* species reveals four different phenotypes. *Appl. Environ. Microbiol.* 75:454–61

Fan Y, Pedersen O. 2020. Gut microbiota in human metabolic health and disease. *Nat. Rev. Microbiol.* 19:55–71

FDA (US Food Drug Adm.). 2016. Food labeling: revision of the nutrition and supplement facts labels. 81 Fed. Reg. 33,741 (May 27) (codified at 21 C.F.R. 101)

Ferrari P, Rinaldi S, Jenab M, Lukanova A, Olsen A, et al. 2013. Dietary fiber intake and risk of hormonal receptor-defined breast cancer in the European Prospective Investigation into Cancer and Nutrition study. *Am. J. Clin. Nutr.* 97:344–53

Fitzgerald CB, Shkoporov AN, Sutton TDS, Chaplin AV, Velayudhan V, et al. 2018. Comparative analysis of *Faecalibacterium prausnitzii* genomes shows a high level of genome plasticity and warrants separation into new species-level taxa. *BMC Genom.* 19:931

Flint HJ. 2020. How gut micro-organisms make use of available carbohydrates. In *Why Gut Microbes Matter*, pp. 81–96. Cham, Switz.: Springer

Flint HJ, Scott KP, Duncan SH, Louis P, Forano E. 2012. Microbial degradation of complex carbohydrates in the gut. *Gut Microbes* 3:289–306

Fuhren J, Rösch C, ten Napel M, Schols HA, Kleerebezem M. 2020. Synbiotic matchmaking in *Lactobacillus plantarum*: substrate screening and gene–trait matching to characterize strain-specific carbohydrate utilization. *Appl. Environ. Microbiol.* 86:e01081-20

Gaulke CA, Sharpton TJ. 2018. The influence of ethnicity and geography on human gut microbiome composition. *Nat. Med.* 24:1495–96

Ghaffari P, Shoaie S, Nielsen LK. 2022. Irritable bowel syndrome and microbiome: switching from conventional diagnosis and therapies to personalized interventions. *J. Transl. Med.* 20:173

Gibbons SM, Gurry T, Lampe JL, Chakrabarti A, Dam V. 2022. Perspective: leveraging the gut microbiota to predict personalized responses to dietary, prebiotic, and probiotic interventions. *Adv. Nutr.* 13:1450–61

Gill SK, Rossi M, Bajka B, Whelan K. 2020. Dietary fibre in gastrointestinal health and disease. *Nat. Rev. Gastroenterol. Hepatol.* 18:101–16

Goh YJ, Klaenhammer TR. 2015. Genetic mechanisms of prebiotic oligosaccharide metabolism in probiotic microbes. *Annu. Rev. Food Sci. Technol.* 6:137–56

Griffin NW, Ahern PP, Cheng J, Heath AC, Ilkayeva O, et al. 2017. Prior dietary practices and connections to a human gut microbial metacommunity alter responses to diet interventions. *Cell Host Microbe* 21:84–96

Groussin M, Poyet M, Sistiaga A, Kearney SM, Moniz K, et al. 2021. Elevated rates of horizontal gene transfer in the industrialized human microbiome. *Cell* 184:2053–67

Gupta VK, Kim M, Bakshi U, Cunningham KY, Davis JM, et al. 2020. A predictive index for health status using species-level gut microbiome profiling. *Nat. Commun.* 11:4635

Gurry T, Gibbons SM, Nguyen LTT, Kearney SM, Ananthakrishnan A, et al. 2018. Predictability and persistence of prebiotic dietary supplementation in a healthy human cohort. *Sci. Rep.* 8:12699

Gurry T, Nguyen LTT, Yu X, Alm EJ. 2021. Functional heterogeneity in the fermentation capabilities of the healthy human gut microbiota. *PLOS ONE* 16:e0254004

Hamaker BR, Tuncil YE. 2014. A perspective on the complexity of dietary fiber structures and their potential effect on the gut microbiota. *J. Mol. Biol.* 426:3838–50

Han W, Ye Y. 2019. A repository of microbial marker genes related to human health and diseases for host phenotype prediction using microbiome data. *Pac. Symp. Biocomput.* 24:236–47

Harvie R, Chanyi RM, Burton JP, Schultz M. 2017. Using the human gastrointestinal microbiome to personalize nutrition advice: Are registered dietitian nutritionists ready for the opportunities and challenges? *J. Acad. Nutr. Diet.* 117:1865–69

Healey G, Murphy R, Butts C, Brough L, Whelan K, Coad J. 2018. Habitual dietary fibre intake influences gut microbiota response to an inulin-type fructan prebiotic: a randomised, double-blind, placebo-controlled, cross-over, human intervention study. *Br. J. Nutr.* 119:176–89

Hitch TCA, Hall LJ, Walsh SK, Leventhal GE, Slack E, et al. 2022. Microbiome-based interventions to modulate gut ecology and the immune system. *Mucosal Immunol.* 15:1095–113

Hjorth MF, Blædel T, Bendtsen LQ, Lorenzen JK, Holm JB, et al. 2018. *Prevotella*-to-*Bacteroides* ratio predicts body weight and fat loss success on 24-week diets varying in macronutrient composition and dietary fiber: results from a post-hoc analysis. *Int. J. Obes.* 43:149–57

Holmes ZC, Villa MM, Durand HK, Jiang S, Dallow EP. 2022. Microbiota responses to different prebiotics are conserved within individuals and associated with habitual fiber intake. *Microbiome* 10:114

Holscher HD. 2017. Dietary fiber and prebiotics and the gastrointestinal microbiota. *Gut Microbes* 8:172–84
Holscher HD, Bauer LL, Gourineni V, Pelkman CL, Fahey GC, Swanson KS. 2015. Agave inulin supplementation affects the fecal microbiota of healthy adults participating in a randomized, double-blind, placebo-controlled, crossover trial. *J. Nutr.* 145:2025–32
Hughes RL, Kable ME, Marco M, Keim NL. 2019a. The role of the gut microbiome in predicting response to diet and the development of precision nutrition models. Part II. Results. *Adv. Nutr.* 10:979–98
Hughes RL, Marco ML, Hughes JP, Keim NL, Kable ME. 2019b. The role of the gut microbiome in predicting response to diet and the development of precision nutrition models. Part I. Overview of current methods. *Adv. Nutr.* 10:953–78
Iadanza E, Fabbri R, Bašić-Čičak D, Amedei A, Telalovic JH. 2020. Gut microbiota and artificial intelligence approaches: a scoping review. *Health Technol.* 10:1343–58
Inst. Med. 2005. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids*. Washington, DC: Natl. Acad.
Jie Z, Yu X, Liu Y, Sun L, Chen P, et al. 2021. The baseline gut microbiota directs dieting-induced weight loss trajectories. *Gastroenterology* 160:2029–42
Joglekar P, Sonnenburg ED, Higginbottom SK, Earle KA, Morland C, et al. 2018. Genetic variation of the SusC/SusD homologs from a polysaccharide utilization locus underlies divergent fructan specificities and functional adaptation in *Bacteroides thetaiotaomicron* strains. *mSphere* 3:00185
Johnson AJ, Vangay P, Al-Ghalith GA, Hillmann BM, Ward TL, et al. 2019. Daily sampling reveals personalized diet–microbiome associations in humans. *Cell Host Microbe* 25:789–802
Johnson AJ, Zheng JJ, Kang JW, Saboe A, Knights D, Zivkovic AM. 2020. A guide to diet–microbiome study design. *Front. Nutr.* 7:79
Johnson JS, Spakowicz DJ, Hong BY, Petersen LM, Demkowicz P, et al. 2019. Evaluation of 16S rRNA gene sequencing for species and strain-level microbiome analysis. *Nat. Commun.* 10:5029
Karlsson FH, Tremaroli V, Nookaew I, Bergström G, Behre CJ, et al. 2013. Gut metagenome in European women with normal, impaired and diabetic glucose control. *Nature* 498:99–103
Katagiri R, Goto A, Sawada N, Yamaji T, Iwasaki M, et al. 2020. Dietary fiber intake and total and cause-specific mortality: the Japan Public Health Center–based prospective study. *Am. J. Clin. Nutr.* 111:1027–35
Katoh T, Ojima MN, Sakanaka M, Ashida H, Gotoh A, Katayama T. 2020. Enzymatic adaptation of *Bifidobacterium bifidum* to host glycans, viewed from glycoside hydrolyases and carbohydrate-binding modules. *Microorganisms* 8:481
Kavitha KR, Ram AV, Anandu S, Karthik S, Kailas S, Arjun NM. 2018. PCA-based gene selection for cancer classification. In *2018 IEEE International Conference on Computational Intelligence and Computing Research*. Piscataway, NJ: IEEE
Kim CC, Healey GR, Kelly WJ, Patchett ML, Jordens Z, et al. 2019. Genomic insights from *Monoglobus pectinilyticus*: a pectin-degrading specialist bacterium in the human colon. *ISME J.* 13:1437–56
Klimenko NS, Tyakht AV, Popenko AS, Vasiliev AS, Altukhov IA, et al. 2018. Microbiome responses to an uncontrolled short-term diet intervention in the frame of the Citizen Science Project. *Nutrients* 10:576
Kolida S, Meyer D, Gibson GR. 2007. A double-blind placebo-controlled study to establish the bifidogenic dose of inulin in healthy humans. *Eur. J. Clin. Nutr.* 61:1189–95
Kong C, Faas MM, de Vos P, Akkerman R. 2020. Impact of dietary fibers in infant formulas on gut microbiota and the intestinal immune barrier. *Food Funct.* 11:9445–67
Koropatkin NM, Cameron EA, Martens EC. 2012. How glycan metabolism shapes the human gut microbiota. *Nat. Rev. Microbiol.* 10:323–35
Korpela K, Flint HJ, Johnstone AM, Lappi J, Poutanen K, et al. 2014. Gut microbiota signatures predict host and microbiota responses to dietary interventions in obese individuals. *PLOS ONE* 9:e90702
Kovatcheva-Datchary P, Nilsson A, Akrami R, Lee YS, De Vadder F, et al. 2015. Dietary fiber–induced improvement in glucose metabolism is associated with increased abundance of *Prevotella*. *Cell Metab.* 22:971–82
Kundi ZM, Lee JC-Y, Pihlajamäki J, Chan CB, Leung KS, et al. 2021. Dietary fiber from oat and rye brans ameliorate Western diet–induced body weight gain and hepatic inflammation by the modulation of short-chain fatty acids, bile acids, and tryptophan metabolism. *Mol. Nutr. Food Res.* 65:1900580

Lagier JC, Dubourg G, Million M, Cadoret F, Bilen M, et al. 2018. Culturing the human microbiota and culturomics. *Nat. Rev. Microbiol.* 16:540–50

Leeming ER, Louca P, Gibson R, Menni C, Spector TD, Le Roy CI. 2021. The complexities of the diet-microbiome relationship: advances and perspectives. *Genome Med*. 13:10

Liu S, Fang Z, Wang H, Zhai Q, Hang F, et al. 2021. Gene–phenotype associations involving human-residential bifidobacteria (HRB) reveal significant species- and strain-specificity in carbohydrate catabolism. *Microorganisms* 9:883

Liu X, Yang W, Petrick JL, Liao LM, Wang W, et al. 2021. Higher intake of whole grains and dietary fiber are associated with lower risk of liver cancer and chronic liver disease mortality. *Nat. Commun.* 12:6388

Liu Z, de Vries B, Gerritsen J, Smidt H, Zoetendal EG. 2020. Microbiome-based stratification to guide dietary interventions to improve human health. *Nutr. Res.* 82:1–10

Lockwood MB, Green SJ. 2020. Clinical care is evolving: the microbiome for advanced practice nurses. *J. Am. Assoc. Nurse Pract.* 32:290–92

Lombard V, Golaconda Ramulu H, Drula E, Coutinho PM, Henrissat B. 2014. The carbohydrate-active enzymes database (CAZy) in 2013. *Nucleic Acids Res*. 42:D490–95

Loomba R, Seguritan V, Li W, Long T, Klitgord N, et al. 2017. Gut microbiome–based metagenomic signature for non-invasive detection of advanced fibrosis in human nonalcoholic fatty liver disease. *Cell Metab*. 25:1054–62

Ma C, Wasti S, Huang S, Zhang Z, Mishra R, et al. 2020. The gut microbiome stability is altered by probiotic ingestion and improved by the continuous supplementation of galactooligosaccharide. *Gut Microbes* 12:e1785252

Magne F, Gotteland M, Gauthier L, Zazueta A, Pesoa S, et al. 2020. The Firmicutes/Bacteroidetes ratio: a relevant marker of gut dysbiosis in obese patients? *Nutrients* 12:1474

Makki K, Deehan EC, Walter J, Bäckhed F. 2018. The impact of dietary fiber on gut microbiota in host, health and disease. *Cell Host Microbe* 23:705–15

Maldonado-Gómez MX, Martínez I, Bottacini F, O'Callaghan A, Ventura M, et al. 2016. Stable engraftment of *Bifidobacterium longum* AH1206 in the human gut depends on individualized features of the resident microbiome. *Cell Host Microbe* 20:515–26

Mallick H, Franzosa EA, McIver LJ, Banerjee S, Sirota-Madi A, et al. 2019. Predictive metabolomic profiling of microbial communities using amplicon or metagenomic sequences. *Nat. Commun.* 10:3136

Mancabelli L, Milani C, Lugli GA, Turroni F, Ferrario C, et al. 2017. Meta-analysis of the human gut microbiome from urbanized and pre-agricultural populations. *Environ. Microbiol.* 19:1379–90

Martínez I, Kim J, Duffy PR, Schlegel VL, Walter J. 2010. Resistant starches types 2 and 4 have differential effects on the composition of the fecal microbiota in human subjects. *PLOS ONE* 5:e15046

Martínez I, Stegen JC, Maldonado-Gómez MX, Eren AM, Siba PM, et al. 2015. The gut microbiota of rural Papua New Guineans: composition, diversity patterns, and ecological processes. *Cell Rep*. 11:527–38

Medawar E, Haange SB, Rolle-Kampczyk U, Engelmann B, Dietrich A, et al. 2021. Gut microbiota link dietary fiber intake and short-chain fatty acid metabolism with eating behavior. *Transl. Psychiatry* 11:500

Mendes-Soares H, Raveh-Sadka T, Azulay S, Edens K, Ben-Shlomo Y, et al. 2019. Assessment of a personalized approach to prediction postprandial glycemic responses to food among individuals without diabetes. *JAMA Netw. Open* 2:e188102

Mobeen F, Sharma V, Tulika P. 2018. Enterotype variations of the healthy human gut microbiome in different geographical regions. *Bioinformation* 14:560–73

Moeller AH. 2017. The shrinking human gut microbiome. *Curr. Opin. Microbiol.* 38:30–35

Munoz J, James K, Bottacini F, Van Sinderen D. 2020. Biochemical analysis of cross-feeding behaviour between two common gut commensals when cultivated on plant-derived arabinogalactan. *Microb. Biotechnol.* 13:1733–47

Muñoz Pedrogo DA, Jensen MD, Van Dyke CT, Murray JA, Woods JA, et al. 2018. Gut microbial carbohydrate metabolism hinders weight loss in overweight adults undergoing lifestyle intervention with a volumetric diet. *Mayo Clin. Proc.* 93:1104–10

Nagata N, Nishijima S, Kojima Y, Hisada Y, Imbe K, et al. 2022. Metagenomic identification of microbial signatures predicting pancreatic cancer from a multinational study. *Gastroenterology* 163:222–38

Namkung J. 2020. Machine learning methods for microbiome studies. *J. Microbiol.* 58:206–16
Ndeh D, Gilbert HJ. 2018. Biochemistry of complex glycan depolymerisation by the human gut microbiota. *FEMS Microbiol. Rev.* 42:146–64
Nguyen NK, Deehan EC, Zhang Z, Jin M, Baskota N, et al. 2020. Gut microbiota modulation with long-chain corn bran arabinoxylan in adults with overweight and obesity is linked to an individualized temporal increase in fecal propionate. *Microbiome* 8:118
O'Toole PW, Marchesi JR, Hill C. 2017. Next-generation probiotics: the spectrum from probiotics to live biotherapeutics. *Nat. Microbiol.* 2:17057
Octaria EA, Siswantining T, Bustamam A, Sarwinda D. 2020. Kernel PCA and SVM-RFE based feature selection for classification of dengue microarray dataset. *AIP Conf. Proc.* 2264:030004
Oh H-S, Min U, Jang H, Kim N, Lim J, et al. 2022. Proposal of a health gut microbiome index based on a meta-analysis of Korean and global population datasets. *J. Microbiol.* 60:533–49
Oh TG, Kim SM, Caussy C, Fu T, Guo J, et al. 2020. A universal gut-microbiome-derived signature predicts cirrhosis. *Cell Metab.* 32:878–88
Ojima MN, Yoshida K, Sakanaka M, Jiang L, Odamaki T, Katayama T. 2022. Ecological and molecular perspectives on responders and non-responders to probiotics and prebiotics. *Curr. Opin. Biotechnol.* 73:108–20
Parkar SG, Frost JKT, Rosendale D, Stoklosinski HM, Jobsis CMH, et al. 2021. The sugar composition of the fibre in selected plant foods modulates weaning infants' gut microbiome composition and fermentation metabolites in vitro. *Sci. Rep.* 11:9292
Parnell JA, Reimer RA. 2012. Prebiotic fibres dose-dependently increase satiety hormones and alter Bacteroidetes and Firmicutes in lean and obese JCR:LA-cp rats. *Br. J. Nutr.* 107:601–13
Pasolli E, Truong DT, Malik F, Waldron L, Segata N. 2016. Machine learning meta-analysis of large metagenomic datasets: tools and biological insights. *PLOS Comput Biol.* 12:e1004977
Pisanu S, Palmas V, Madau V, Casula E, Deledda A, et al. 2020. Impact of a moderately hypocaloric Mediterranean diet on the gut microbiota composition of Italian obese patients. *Nutrients* 12:2707
Poeker SA, Geirnaert A, Berchtold L, Greppi A, Krych L, et al. 2018. Understanding the prebiotic potential of different dietary fibers using an in vitro continuous adult fermentation model (PolyFermS). *Sci. Rep.* 8:4318
Probert HM, Apajalahti JHA, Rautonen N, Stowell J, Gibson GR. 2004. Polydextrose, lactitol, and fructo-oligosaccharide fermentation by colonic bacteria in a three-stage continuous culture system. *Appl. Environ. Microbiol.* 70:4505–11
Qu K, Gao F, Guo F, Zou Q. 2019. Taxonomy dimension reduction for colorectal cancer prediction. *Comput. Biol. Chem.* 83:107160
Quince C, Delmont TO, Raguideau S, Alneberg J, Darling AE, et al. 2017. DESMAN: a new tool for de novo extraction of strains from metagenomes. *Genome Biol.* 18:181
Quince C, Nurk S, Raguideau S, James R, Soyer OS, et al. 2021. STRONG: metagenomics strain resolution on assembly graphs. *Genome Biol.* 22:214
Rakoff-Nahoum S, Foster KR, Comstock LE. 2016. The evolution of cooperation within the gut microbiota. *Nature* 533:255–59
Ramos-Romero S, Léniz A, Martínez-Maqueda D, Amézqueta S, Fernández-Quintela A, et al. 2021. Inter-individual variability in insulin response after grape pomace supplementation in subjects at high cardiometabolic risk: role of microbiota and miRNA. *Mol. Nutr. Food Res.* 65:e2000113
Rampelli S, Schnorr SL, Consolandi C, Turroni S, Severgnini M, et al. 2015. Metagenome sequencing of the Hadza hunter-gatherer gut microbiota. *Curr. Biol.* 25:1682–93
Reichardt N, Vollmer M, Holtrop G, Farquharson FM, Wefers D, et al. 2018. Specific substrate-driven changes in human faecal microbiota composition contrast with functional redundancy in short-chain fatty acid production. *ISME J.* 12:610–22
Rivière A, Moens F, Selak M, Maes D, Weckx S, De Vuyst L. 2014. The ability of bifidobacteria to degrade arabinoxylan oligosaccharide constituents and derived oligosaccharides is strain dependent. *Appl. Environ. Microbiol.* 80:204–17
Rivière A, Selak M, Lantin D, Leroy F, De Vuyst L. 2016. Bifidobacteria and butyrate-producing colon bacteria: importance and strategies for their stimulation in the human gut. *Front. Microbiol.* 7:979

Rodriguez J, Hiel S, Neyrinck AM, Le Roy T, Pötgens SA, et al. 2020. Discovery of the gut microbial signature driving the efficacy of prebiotic intervention in obese patients. *Gut* 69:1975–87

Rothschild D, Weissbrod O, Barkan E, Kurilshikov A, Korem T, et al. 2018. Environment dominates over host genetics in shaping human gut microbiota. *Nature* 555:210–15

Saito Y, Shigehisa A, Watanabe Y, Tsukuda N, Moriyama-Ohara K, et al. 2020. Multiple transporters and glycoside hydrolases are involved in arabinoxylan derived oligosaccharide utilization in *Bifidobacterium pseudocatenulatum*. *Appl. Environ. Microbiol.* 86:e01782

Salonen A, Lahti L, Salojärvi J, Holtrop G, Korpela K, et al. 2014. Impact of diet and individual variation on intestinal microbiota composition and fermentation products in obese men. *ISME J.* 8:2218–30

Sandberg J, Kovatcheva-Datchary P, Björck I, Bäckhed F, Nilsson A. 2019. Abundance of gut *Prevotella* at baseline and metabolic response to barley prebiotics. *Eur. J. Nutr.* 58:2365–76

Sanders ME, Benson A, Lebeer S, Merenstein DJ, Klaenhammer TR. 2018. Shared mechanisms among probiotic taxa: implications for general probiotic claims. *Curr. Opin. Biotechnol.* 49:207–16

Schnorr SL, Candela M, Rampelli S, Centanni M, Consolandi C, et al. 2014. Gut microbiome of the Hadza hunter-gatherers. *Nat. Commun.* 5:3654

Schroeder BO, Birchenough GMH, Ståhlman M, Arike L, Johansson MEV, et al. 2018. Bifidobacteria or fiber protects against diet-induced microbiota-mediated colonic mucus deterioration. *Cell Host Microbe* 23:27–40.e7

Schupack DA, Mars RAT, Voelker DH, Abeykoon JP, Kashyap PC. 2022. The promise of the gut microbiome as part of individualized treatment strategies. *Nat. Rev. Gastroenterol. Hepatol.* 19:7–25

Segata N. 2015. Gut microbiome: westernization and the disappearance of intestinal diversity. *Curr. Biol.* 25:R611–13

Sheridan PO, Martin JC, Lawley TD, Browne HP, Harris HMB, et al. 2015. Polysaccharide utilization loci and nutritional specialization in a dominant group of butyrate-producing human colonic Firmicutes. *Microb. Genom.* 2:e000043

Singh RK, Chang H-W, Yan D, Lee KM, Ucmak D, et al. 2017. Influence of diet on the gut microbiome and implications for human health. *J. Transl. Med.* 15:73

So D, Yao CK, Gill PA, Pillai N, Gibson PR, Muir JG. 2021. Screening dietary fibres for fermentation characteristics and metabolic profiles using a rapid in vitro approach: implications for irritable bowel syndrome. *Br. J. Nutr.* 126:208–18

Song S, Song YJ. 2021. Dietary fiber and its source are associated with cardiovascular risk factors in Korean adults. *Nutrients* 13:160

Sonnenburg ED, Smits SA, Tikhonov M, Higginbottom SK, Wingreen NS, et al. 2016. Diet-induced extinctions in the gut microbiota compound over generations. *Nature* 529:212–15

Sonnenburg ED, Sonnenburg JL. 2014. Starving our microbial self: the deleterious consequences of a diet deficient in microbiota-accessible carbohydrates. *Cell Metab.* 20:779–86

Sonnenburg ED, Zheng H, Joglekar P, Higginbottom SK, Firbank SJ, et al. 2010. Specificity of polysaccharide use in intestinal *Bacteroides* species determines diet-induced microbiota alterations. *Cell* 141:1241–52

Sonnenburg JL, Xu J, Leip DD, Chen C-H, Westover BP, et al. 2005. Glycan foraging in vivo by an intestine-adapted bacterial symbiont. *Science* 307:1955–59

Soverini M, Rampelli S, Turroni S, Schnorr SL, Quercia S, et al. 2016. Variations in the post-weaning human gut metagenome profile as result of *Bifidobacterium* acquisition in the Western microbiome. *Front. Microbiol.* 7:1058

Soverini M, Turroni S, Biagi E, Quercia S, Brigidi P, et al. 2017. Variation of carbohydrate-active enzyme patterns in the gut microbiota of Italian healthy subjects and type 2 diabetes patients. *Front. Microbiol.* 8:2079

Sun Y, Fan X, Zhao J. 2022. Development of colorectal cancer detection and prediction based on gut microbiome big data. *Med. Microecol.* 12:100053

Swanson KS, de Vos WM, Martens EC, Gilbert JA, Menon RS, et al. 2020. Effect of fructans, prebiotics and fibres on the human gut microbiome assessed by 16S rRNA–based approaches: a review. *Benef. Microbes* 11:101–29

Tamburini F, Maghini D, Oduaran OH, Brewster R, Hulley MR, et al. 2022. Short- and long-read metagenomics of urban and rural South African gut microbiomes reveal a transitional composition and undescribed taxa. *Nat. Comm.* 13:926

Tanes C, Bittinger K, Gao Y, Friedman ES, Nessel L, et al. 2021. Role of dietary fiber in the recovery of the human gut microbiome and its metabolome. *Cell Host Microbe* 29:394–407

Thomas AM, Manghi P, Asnicar F, Pasolli E, Armanini F, et al. 2019. Metagenomic analysis of colorectal cancer datasets identifies cross-cohort microbial diagnostic signatures and a link with choline degradation. *Nat. Med.* 25:667–78

Topçuoğlu BD, Lesniak NA, Ruffin MT, Wiens J, Schloss PD. 2020. A framework for effective application of machine learning to microbiome-based classification problems. *mBio* 11:e00434

Tuohy KM, Kolida S, Lustenberger AM, Gibson GR. 2001. The prebiotic effects of biscuits containing partially hydrolysed guar gum and fructo-oligosaccharides—a human volunteer study. *Br. J. Nutr.* 86:341–48

Turroni F, Strati F, Foroni E, Serafini F, Duranti S, et al. 2012. Analysis of predicted carbohydrate transport systems encoded by *Bifidobacterium bifidum* PRL2010. *Appl. Environ. Microbiol.* 78:5002–12

USDA Agric. Res. Serv. 2021. *Usual nutrient intake from food and beverages, by gender and age. What we eat in America: NHANES 2015–2018*. Data Tables, USDA Agric. Res. Serv., Beltsville, MD

Valdez-Palomares F, Nambo-Venegas R, Uribe-García J, Mendoza-Vargas A, Granados-Portillo O, et al. 2021. Intestinal microbiota fingerprint in subjects with irritable bowel syndrome responders to a low FODMAP diet. *Food Funct.* 12:3206–18

Van Den Abbeele P, Duysburgh C, Ghyselinck J, Goltz S, Berezhnaya Y, et al. 2021. Fructans with varying degree of polymerization enhance the selective growth of *Bifidobacterium animalis* subsp. *lactis* BB-12 in the human gut microbiome in vitro. *Appl. Sci.* 11:598

Van Rossum T, Ferretti P, Maistrenko OM, Bork P. 2020. Diversity within species: interpreting strains in microbiomes. *Nat. Rev. Microbiol.* 18:491–506

Vangay P, Hillmann BM, Knights D. 2019. Microbiome Learning Repo (ML Repo): a public repository of microbiome regression and classification tasks. *Gigascience* 8:giz042

Vangay P, Johnson AJ, Ward TL, Al-Ghalith GA, Shields-Cutler RR, et al. 2018. US immigration westernizes the human gut microbiome. *Cell* 175:962–72

Vatanen T, Plichta DR, Somani J, Münch PC, Arthur TD, et al. 2019. Genomic variation and strain-specific functional adaptation in the human gut microbiome during early life. *Nat. Microbiol.* 4:470–79

Villa MM, Bloom RJ, Silverman JD, Durand HK, Jiang S, et al. 2020. Interindividual variation in dietary carbohydrate metabolism by gut bacteria revealed with droplet microfluidic culture. *mSystems* 5:e00864

Wang Q, Wang K, Wu W, Giannoulatou E, Ho JWK, Li L. 2019. Host and microbiome multi-omics integration: applications and methodologies. *Biophys. Rev.* 11:55–65

Wang S, Xiao Y, Tian F, Zhao J, Zhang H, et al. 2020. Rational use of prebiotics for gut microbiota alterations: specific bacterial phylotypes and related mechanisms. *J. Funct. Foods* 66:103838

Watanabe Y, Saito Y, Hara T, Tsukuda N, Aiyama-Suzuki Y, et al. 2021. Xylan utilisation promotes adaptation of *Bifidobacterium pseudocatenulatum* to the human gastrointestinal tract. *ISME Commun.* 1:62

Wenzel TJ, Gates EJ, Ranger AL, Klegeris A. 2020. Short-chain fatty acids (SCFAs) alone or in combination regulate select immune functions of microglia-like cells. *Mol. Cell. Neurosci.* 105:103493

Wexler AG, Goodman AL. 2017. An insider's perspective: *Bacteroides* as a window into the microbiome. *Nat. Microbiol.* 2:17026

Ye S, Shah BR, Li J, Liang H, Zhan F, et al. 2022. A critical review on interplay between dietary fibers and gut microbiota. *Trends Food Sci. Technol.* 124:237–49

Yoshida K, Hirano R, Sakai Y, Choi M, Sakanaka M, et al. 2021. *Bifidobacterium* response to lactulose ingestion in the gut relies on a solute-binding protein–dependent ABC transporter. *Commun. Biol.* 4:541

Yu D, Zhao L, Zhao W. 2020. Status and trends in consumption of grains and dietary fiber among Chinese adults (1982–2015). *Nutr. Rev.* 78(Suppl. 1):43–53

Ze X, Duncan SH, Louis P, Flint HJ. 2012. *Ruminococcus bromii* is a keystone species for the degradation of resistant starch in the human colon. *ISME J.* 6:1535–43

Zeevi D, Korem T, Zmora N, Halpern Z, Elinav E, et al. 2015. Personalized nutrition by prediction of glycemic responses. *Cell* 163:1079–94

Zhernakova A, Kurilshikov A, Bonder MJ, Tigchelaar EF, Schirmer M, et al. 2016. Population-based metagenomics analysis reveals markers for gut microbiome composition and diversity. *Science* 352:565–69

Zhou Y-H, Gallins P. 2019. A review and tutorial of machine learning methods for microbiome host trait prediction. *Front. Genet.* 10:579