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Annual Review of Food Science and Technology
Predicting Personalized
Responses to Dietary Fiber
Interventions: Opportunities
for Modulation of the Gut
Microbiome to Improve Health

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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

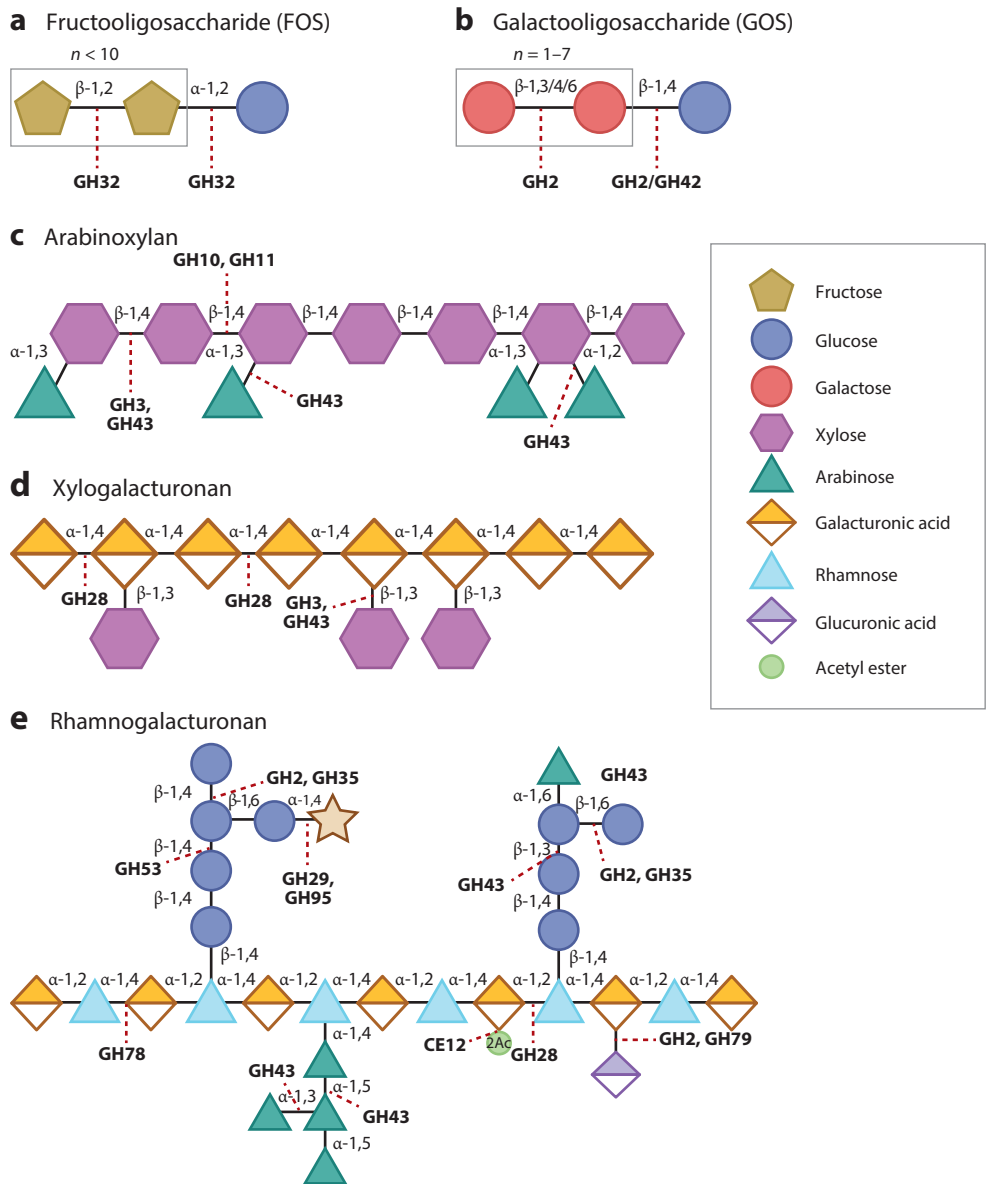


Figure 1

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 *Butyrivibrio* 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	<i>Bifidobacterium</i> abundance	9	9	Davis et al. (2010, 2011)
Resistant starch 4	Healthy	<i>Bifidobacterium</i> abundance	6	4	Martínez et al. (2010)
Resistant starch 2			5	5	
Biscuits containing partially hydrolyzed guar gum and fructooligosaccharides	Healthy	<i>Bifidobacterium</i> abundance	27 ^a	4	Tuohy et al. (2001)
Inulin	Healthy	<i>Bifidobacterium</i> abundance	20	10	Kolida et al. (2007)

^a15 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,

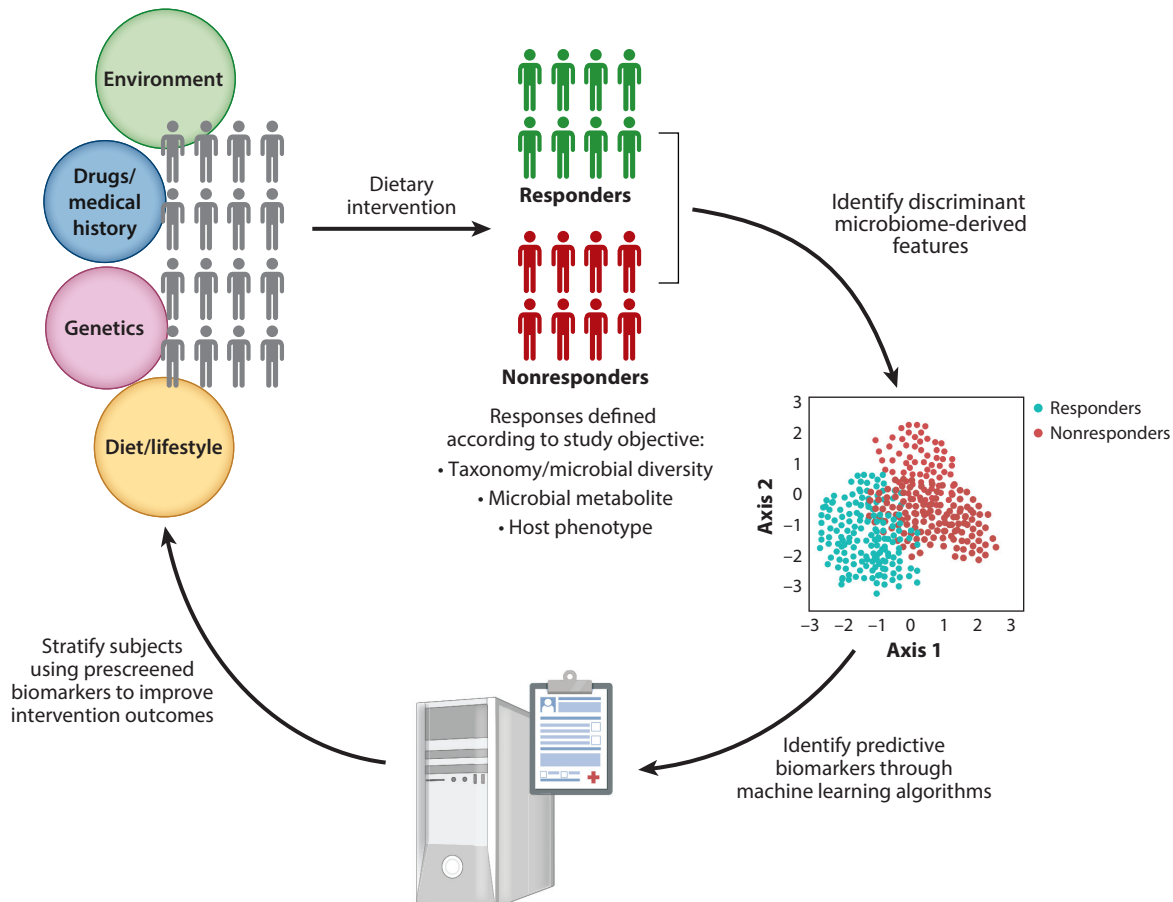


Figure 2

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 Pedrego et al. (2018) and Rodriguez et al. (2020) evaluated responses of obese patients toward lifestyle and dietary interventions by measuring

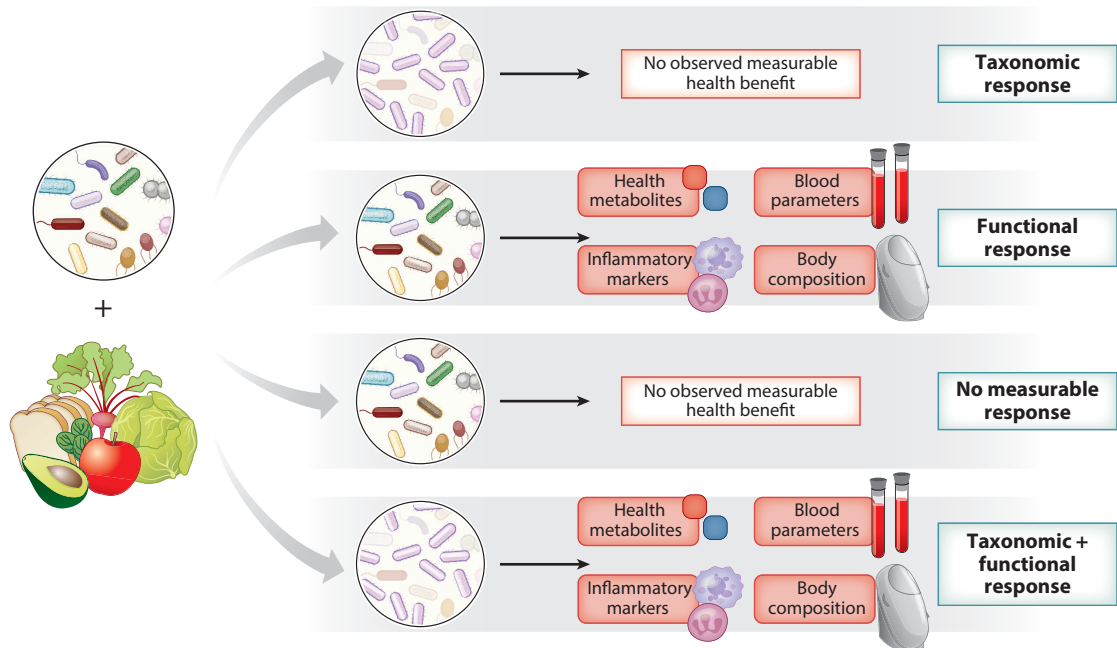


Figure 3

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 *Lactiacaseibacillus 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, Rivièrè 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, Turrone 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 pre-labeled 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.

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