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The next generation beneficial actions of novel probiotics as potential therapeutic targets and prediction tool for metabolic diseases

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Abstract

The prevalence of metabolic disease has rising and affected over 1,000 million populations globally. Since the metabolic disease and its related complication are board, it has become the major health hazard of modern world. However, Long term medication of metabolic disease may cause serious side effects and risk for adverse health problems. Recently, emerging studies focus on exploring the mechanistic details of metabolic state in disease development and progression. Gut bacteria ecosystem was considered to play a pivotal role in regulating energy homeostasis and great associated with the development of metabolic disease. Accumulated evidences indicated that *Akkermansia muciniphila*, *Faecalibacterium prausnitzii*, and *Roseburia hominis* improve the balance of the microecology in the intestine of the host and have positive effects on enhancing nutrients absorption. Hence, the novel probiotics as therapeutic target to modify gut microbiota generally focus on improving microbiota dysbiosis, and offers new prospects for treating metabolic disease. In the present review, we discuss the significant roles and regulatory properties of specific bacterium in the context of intestinal microbial balance, explores the kinds of harmful/beneficial bacteria that were likely to act as indicator for metabolic disease. Further proposed a stepwise procedure in the basis of sequencing technology with that of innovative option to reestablish the microbial equilibrium and prevent metabolic disease.

Keywords: Disease prediction, Metabolic disease, Microbiota, Novel probiotics

1. Introduction

The term of metabolic syndrome (MetS) refers to a constellation of associated metabolic diseases states, characterized by insulin resistance (IR), dyslipidemia, hyperglycemia, and high blood pressure, which resultant type 2 diabetes mellitus (T2DM), central obesity, hypertension, and increased the risk of coronary artery disease (CAD), chronic renal failure, and malignant development. Since various diagnostic criteria of MetS are proposed, the incidence and impact are differing from

countries. The reported epidemic of the syndrome was according to the consensus definitions, age, gender, and ethnicity [1]. In addition, secondary lifestyle and socioeconomic strata were suggested to influence prevalence across the aforementioned physiological factors. In generally, the global prevalence of MetS among the adult population were reported to range between 20 and 25% across countries and region [2]. Besides, the western dietary patterns were strongly correlated with developing metabolic abnormalities and a main risk factor for chronic cardiometabolic syndrome.

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Interestingly, the gut microbiota, *via* extracting energy from the human diet by which it may affect host health that was supporting the aforementioned associations was recently emphasized.

Collectively, the metabolic diseases is a multifactorial and multiorgan pathophysiologic state, which were linked to genetic architecture, healthy behavior change, and also intensely affected by gastrointestinal tract microbial ecosystem, is now been considered as a pivotal role in metabolic health and diseases, acting as a second genome [3]. Emerging studies proposed that gut microbiota contributed to a variety of physiological functions impacting human metabolic balance and disorders. The genome-wide association study have shown that gut microbiota diversity is involved in core function, including the modulation of nutrients and energy harvest efficiency, maintenance of intestinal epithelial barrier functions, stimulation of host immune response to discriminate commensals from pathogens. Two predominant bacterial phyla have been implicated in the composition of human gut microbiota: Bacteroidetes and Firmicutes. The population ration of these phyla (F/B ratio) is widely accepted as a potential indicator for maintaining gut homeostasis. The increased F/B ratio, expanding population of Firmicutes phyla and/or contracting population of Bacteroidetes phyla in individuals, which was demonstrated to characterize the dysbiosis signature of host gut microbiota. Since specific gut microbiota composition revealed high-risk rates for gastrointestinal dysfunction and leads to devastating metabolic consequence, the develop strategies for preventing perturbation of microbiota communication is now becomes a major focus. In addition, a rich diversity in gut microbiota and higher abundant in probiotics is conducive to enrich microbial consortium that are principally produced primary metabolites, of which short-chain fatty acids (SCFAs) directly or indirectly meliorated peripheral inflammation, impacted immune cells function, act through G protein-coupled-receptors signaling activation. Indeed, the balance of the intestinal microbial community is crucial to promote an overall homeostasis condition of human host achieving global health goals.

Although both scientific and commercial advances for probiotics that are commonly restricted to specific strain or species mainly include *Lactobacillus* and *Bifidobacteria*, are generally identified as traditional probiotics, other novel candidate therapeutic probiotics have yet been fully developed up to now, and which are more likely to establish the preferable mechanism for deeper investigation.

Among recent evidences on metagenome sequencing based analysis, the SCFAs-producing bacteria have been referred to as potential candidates for the application of next generation to treat or avert, even cure for metabolic diseases of human beings. Besides, advanced molecular microbial profiling technologies generated massive information about the intestine ecological dynamics impact in metabolic pathological processes. In order to manage the high-dimensional data, the artificial intelligence in machine learning technology would be helpful to boost information processing. Although new nucleic acid sequencing tool and powerful algorithms enable us to deeper understand microbial community, the complex interaction between intestine microbiome and the host disease state is still a challenge. In the present review, we aim to provide an overview of recent literature that focus on intestinal ecosystem dynamics in the host with metabolic disease, and helping guide further study will clarify the potential for and support a novel predictive model for metabolic disease development to promote and achieve anti-metabolic derangement. The systemic framework based on sample collection, NGS analysis, data connection, and final metabolic diseases risk identification (Fig. 1).

2. Type-2 diabetes mellitus

The resistance of peripheral tissue including muscle, liver, and adipose tissue to insulin actions, which forced islet β cell to increase the secretion of insulin was mainly observed in T2DM. The detailed mechanistic pathway and major risk factors for T2DM is well established. Currently, scientific research aims to verify the significance of other factors involved, such as gut microbiota and its secondary metabolites in T2DM development. The first human study by Larsen et al. demonstrated a significant difference across healthy and T2DM subjects in terms of the composition of intestinal microbiome [4]. Furthermore, faecal microbiota composition profiles from 18 individuals with/or without T2DM, characterized by a substantial reduction of *Firmicutes* phyla and increasing the relative abundance of *Bacteroidetes* phyla and *Proteobacteria* phyla in T2DM patients. Although metagenome-wide association analysis have determined the *Bacteroidetes* and *Firmicutes* were major phyla in human gastrointestinal tract, the gut dysbiosis caused by other phyla such as *Actinobacteria*, *Proteobacteria*, and *Fusobacteria* promote susceptibility to insulin resistance, typical pathological condition of

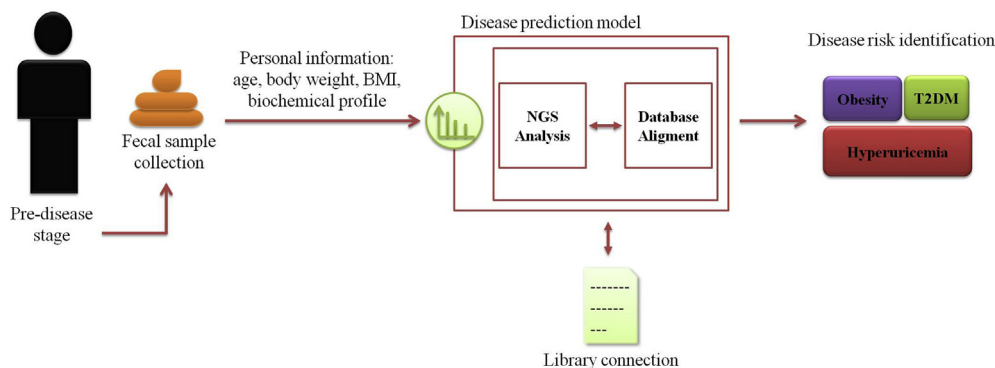


Fig. 1. Graphical abstract of the proposed working model system. The systemic framework based on sample collection, NGS analysis, data connection, and final metabolic diseases risk identification.

diabetes [5]. In the context, emerging human data and animal's model focus on characterizing properties of the microbiome in T2DM, and further evaluate the relative abundance of specific bacteria taxa to identify their relationship with this metabolic condition. Recently, Chatelier and the colleagues described low gene count of *Roseburia intestinalis* and *Faecalibacterium prausnitzii* were founded in individuals with T2DM, as well as elevated oxidative stress, inflammatory status, and gut leakage. Deeper, microbiom taxonomic and functional profiles from 784 gut metagenomes showed that non-diabetic treated T2D patients ($n = 106$) exhibited significantly decreased in butyrate-producing species (*Roseburia* spp., *Subdoligranulum* spp., and *Clostridiales* spp.) as compared to non-diabetic participants ($n = 554$). According to meta-analysis pipeline and validation in all datasets, the abundance of genus *Akkermansia* was 3-fold increased after metformin treatment, which was in consisted

with genus *Escherichia* [6]. Table 1 summarizes the findings of gut dysbiosis in the abundance and richness from both preclinical animal models and human trail of T2DM.

3. Obesity

Western dietary habit and sedentary lifestyle invariably cause rapid induction of IR and hyperglycemia, as well as obesity. The resident microbiota was extensively considered as an indispensable enteroendocrine organ in the host functioning with properties of energy harvest, especially for the context to develop overweight and obesity. Preliminary evidence from animal studies, the intestinal microbiota was able to affect weight gain/or lose, and associated with body composition. Based on studies of germ-free mice, even microbial inoculation for functional microbiome research has linked the association between intestinal microbiota and

Table 1. Main findings of gut microbial populations changing associated with T2DM.

Subjects' Characteristics	Implicated microbiota	References
Female participants with T2DM (Denmark)	phylum <i>Firmicutes</i> ↓/class <i>Clostridia</i> ↓/class <i>Betaproteobacteria</i> ↑/genus <i>Roseburia</i> ↓	[4]
Male participants with T2DM (European)	<i>Clostridium clostridioforme</i> ↑/ <i>Clostridium hathewayi</i> ↑/ <i>Bacteroides intestinalis</i> ↓	[41]
Participants with T2DM (Chinese)	<i>Bacteroides caccae</i> ↑/ <i>Clostridium hathewayi</i> ↑/ <i>Clostridium ramosum</i> ↑/ <i>Clostridium symbiosum</i> ↑/ <i>Eggerthella lenta</i> ↑/ <i>Escherichia coli</i> ↑/ <i>Clostridiales</i> sp. SS3/4 ↓/ <i>Eubacterium rectale</i> ↓/ <i>Faecalibacterium prausnitzii</i> ↓/ <i>Roseburia intestinalis</i> ↓/ <i>Roseburia inulinivorans</i> ↓	[30]
Male <i>db/db</i> mice (8-week-old)	family <i>Bacteroidaceae</i> ↓/family <i>Prevotellaceae</i> ↓/genus <i>Clostridium</i> ↓/phylum <i>Verrucomicrobia</i> ↑/species <i>Lactobacillus reuteri</i> ↑	[42]
Tsumura Suzuki obese diabetes mice (12-week-old)	<i>Clostridium ruminantium</i> ↑/ <i>Clostridium celatum</i> ↑/ <i>Ruminococcus callidus</i> ↑/ <i>Clostridium colinum</i> ↓	[43]
Participants with pre-DM/T2DM (Chinese)	<i>Akkermansia muciniphila</i> ATCCBAA-835 ↓/ <i>Faecalibacterium prausnitzii</i> L2-6 ↓/ <i>Verrucomicrobiae</i> ↓	[44]
Participants with T2DM (Poland)	genus <i>Roseburia</i> ↓/family <i>Clostridiaceae</i> ↓/genus <i>Ruminococcus</i> ↑/family <i>Enterobacteriaceae</i> ↑	[45]

obesity. Colonization of germ-free C57BL/6 mice with conventional microbiota harvested from cecum as a consequence of IR and total body fat elevated approximately to the level of donor subjects. Intriguingly, the increased body fat components were in consist with it reflected increased energy output and decreased consumption despite markedly less food intake. As discussed suggested, the intestinal microbiota may served as mediators in energy metabolism [7]. Excepted for vitamin synthesis, saccharolytic fermentation carried out by the intestinal microbiota produced a variety of microbial metabolites such as SCFA, mediated by predominant species including *Roseburia*, *Lactobacillus*, *Bifidobacterium*, and *Faecalibacterium*. Concentration of these microbial-produced metabolites was recently recognized to correlate with elevated fat content and obesity. Remely and the colleagues reported that obese participants underwent nutrients counseling and extra glucagon-like peptide intervention exhibited an increased trend in abundance of *Faecalibacterium prausnitzii* and epigenetic methylation of FFAR3 and LINE-1 [8]. The results were consisted with other comparative study between obese and lean participants, and showed that *Faecalibacterium prausnitzii* level and systemic inflammatory markers such as fecal calprotectin and plasma C-reactive protein were increased in obese [9]. Similar to

animal model of diet-induced obesity, a significant reduction in butyrate-producing probiotics related to *Roseburia* app. and *Eubacterium rectale* in relation to energy harvested ability of subjects with obesity when compared to lean ones [10]. Moreover, the prebiotic properties of *Roseburia* spp. was demonstrated to along with reduced IL-6, MCP-1, subcutaneous adipose fat, and downregulated genes expression involved in hepatic cholesterol synthesis (C/EBP α , FAT/CD36, aP2, and LPL) [11]. Overall, the main characteristic of microbiota composition is emphasized by the depletion and repletion resultant. The vast majority of those phenomenons strongly indicated that obese phenotype exhibit a significant shift in the richness of helpful and potentially pathogenic bacteria in compared with lean phenotype (Table 2).

4. Hyperuricemia

Although T2DM and obesity were most prevalent metabolic diseases and main health concerns of modern life nowadays. The common Western dietary pattern is characterized by highly saturated fatty acid and sugar, especially fructose with the form of corn syrup in foods and beverages. Accumulated evidences demonstrated that high fructose consumption eventually leads to elevation in

Table 2. Main findings of gut microbial populations changing associated with obesity.

Subjects' Characteristics	Implicated microbiota	References
Pregnant Participants with obesity (Finland)	<i>Bacteroides</i> group \uparrow / <i>Staphylococcus</i> group \uparrow	[46]
Participants with obesity (Germany)	<i>Bifidobacterium</i> \downarrow / <i>Clostridium leptum</i> \downarrow / <i>Methanobrevibacter</i> \downarrow / <i>Firmicutes</i> \downarrow / <i>Bacteroidetes</i> \uparrow	[47]
Participants with obesity (Chinese)	<i>Clostridium perfringens</i> \downarrow / <i>Bacteroides</i> \downarrow	[48]
Children participants with obesity (India)	<i>Faecalibacterium prausnitzii</i> \uparrow	[49]
Children participants with obesity (Belgium)	<i>Bacteroides vulgates</i> \downarrow / <i>Lactobacillus</i> spp. \uparrow	[50]
Adolescents participants with overweight/ and obesity (Spain)	<i>Bacteroides fragilis</i> \uparrow / <i>Lactobacillus</i> groups \uparrow / <i>Clostridium coccoides</i> \downarrow / <i>Bifidobacterium longum</i> \downarrow / <i>Bifidobacterium adolescentis</i> \downarrow	[51]
Children participants with obesity (Italy)	family Ruminococcaceae \uparrow /family Bacteroidaceae \downarrow	[52]
Participants with obesity (Chinese)	<i>Akkermansia muciniphila</i> \downarrow / <i>Faecalibacterium prausnitzii</i> \downarrow / <i>Bacteroides uniformis</i> \downarrow / <i>Bacteroides ovatus</i> \downarrow / <i>Ruminococcus torques</i> \uparrow / <i>Fusobacterium ulcerans</i> \uparrow	[53]
Female participants with obesity (Chinese)	<i>Roseburia</i> spp. \downarrow / <i>Lachnospira</i> spp. \downarrow / <i>Clostridiales</i> spp. \downarrow / <i>Faecalibacterium</i> spp. \downarrow /family Lachnospiraceae \downarrow	[54]
Participants with obesity (Germany)	genus Akkermansia \downarrow /genus Dialister \downarrow /genus Prevotella \uparrow /genus Megamonas \uparrow /genus Phascolarctobacterium \uparrow	[55]
Male Sprague-Dawley rats (HFD-induced obesity)	phylum Firmicutes \uparrow /phylum Proteobacteria \uparrow /phylum Actinobacteria \uparrow /phylum Bacteroidetes \downarrow	[56]
Leptin-deficient <i>ob/ob</i> mice (C57BL/6)	<i>Bacteroides</i> \downarrow / <i>Firmicutes</i> \uparrow	[57]
Leptin-deficient <i>ob/ob</i> mice (C57BL/6)	genus Akkermansia \downarrow /genus Dubosiella \downarrow /genus Muribaculaceae \downarrow /genus Turicibacter \uparrow /genus Lactobacillus \uparrow /genus Coriobacteriaceae \uparrow	[58]

Increased *Bacteroides fragilis* group (P = 0.001) and *Lactobacillus* group (P = 0.030) counts, and to decreased *Clostridium coccoides* group (P = 0.028), *Bifidobacterium longum* (P = 0.031), and *Bifidobacterium adolescentis* (P = 0.044) counts.

intestine share same phylotypes in the same patient which believed to involve in the development of CAD [15,16]. A case-control study enrolled 53 participants with advanced CAD and 53 healthy controls to analyze the intestinal microbial alternation between the two groups. The results showed that Chao-1 index, Shannon diversity, and observed number of operational taxonomic units (OTUs) were founded to lower in CAD fecal samples. An alternation was observed in the abundance of *Lachnospiraceae* NK4B4, *Ruminooccus Gauvreauii* were significant lower, while *Ruminooccus gnauvus* was significant higher, and suggested to correlate with CAD progression [17]. Previously, comparative cohort study conducted in 218 participants with atherosclerosis and 187 healthy participants revealed a characteristic alteration in intestinal microbial composition and metabolic functions. The results exhibit a significant reduction in the relative abundance of novel probiotics, including *Roseburia intestinalis* and *Faecalibacterium cf. prausnitzii* in participants with atherosclerosis, as well as other functional modules correlated to atherosclerosis [18]. Trimethylamine N-oxide (TMAO), one toxic metabolite produced by bacteria, is pro-atherogenic in rodent and humans [19]. The intestinal microbial-mediated TMAO production was discovered in genus level including *Clostridium*, *Enterococcus*, *Acinetobacter*, *Citrobacter*, *Anaerococcus*, *Desulfitobacter*, *Streptococcus*, *Desulfovibrio*, *Enterobacteria*, *Escherichia*, *Klebsiella*, *Proteus*, and *Pseudomonas* [20]. Notably, higher *Akkermansia* level was indicated to associated with TMAO production [21]. Although TMAO is widely accepted as marker to the pathogenesis of CAD, other microbial products such as SCFA, LPS, and secondary bile acid along the TMAO cascade are of great interest. The intestinal microbiome alteration that involved in the onset of CAD were summarized in Table 4.

6. Novel potential probiotics: SCFAs-producing bacteria

Metabolic diseases including T2DM, obesity, and hyperuricemia have achieved high proportions that constitute multiple public health concerns confront the human population. Moreover, recent progresses in these metabolic disorders were reported linking to the dramatic change in human intestinal ecosystem diversity. Indeed, the intestinal microbial quantity and richness is considered as a significant marker in host health condition and confronting disease. The metabolic diseases are originated from low-grade inflammation which implicated in a main triggering factor, the bacteria-produced LPS, as its

translocation was restricted to gut epithelial barrier. However, the disruption of gut microbial bio-network leads to downregulation of occluding, claudins, and zonula occludens, proteins that compose epithelial tight-junction, and which eventually causes intestinal mucosal barrier leaking and results in the release of LPS into the systemic circulation. The impaired intestinal permeability promotes LPS translocation that may link to early development of IR and chronic inflammation in germ-free mice model and human subjects [22,23]. The fermented microbial production such as SCFAs, mainly acetate, propionate, and butyrate, were recently demonstrated to exert an anti-inflammatory property, regulated carbohydrates, and fatty acid metabolism [24]. Absorption of SCFAs by intestinal epithelium through specific receptors including monocarboxylate transporters and sodium-coupled monocarboxylate transporters that acts as modulators for maintaining intestinal barrier function. Besides, SCFAs interacts with metabolite-sensing G-protein coupled receptors, thereby stimulating intracellular anti-oxidative and anti-inflammatory pathways. Importantly, a significant observation in both human subject and rodent model with metabolic disease that revealed reduced abundance of dominant SCFAs-producing species, such as *Faecalibacterium prausnitzii* and *Roseburia hominis* in gastrointestinal tract and fecal samples, as well as the SCFAs concentration appear to be reduced when compared with health phenotype. *Roseburia* spp. metabolized complex non-digestible carbohydrate and dominantly produced butyrate during growth under fermentation. Previously, a large clinical trial analyzed the main composition of intestinal microbiota between ulcerative colitis and health participants by using denature gradient gel electrophoresis technique. Interestingly, relative abundance of butyrate-producing bacteria *Roseburia hominis* was founded to significant lower in ulcerative colitis group, and was inversely associated with intestinal inflammation. Base on this observation, Patterson et al. propose that mono-colonization of *Roseburia hominis* may regulate host-microbe cross-talk in germ-free mice. The presents of *Roseburia hominis* in gut result in increase in intestinal barrier integrity, anti-pathogenic activity, and T cell biology that may serve as an anti-inflammatory commensal bacterium [25]. Moreover, depletion of *Roseburia hominis* and *Faecalibacterium prausnitzii* has also been noted in ulcerative colitis and Crohn's disease [26]. To note predominant producer of butyrate in human intestine is *Faecalibacterium prausnitzii*, which has been consistently mentioned as a special degrader of non-digestible dietary substrates. Oral

butyrate supplementation significantly attenuated TNF- α and IL-1 β production as well as macrophage chemoattractant protein-1 expression in white adipose tissue, against HFD-induced obesity and IR in C57BL/6 mice model [27]. In comparison to lean control, obese and T2DM participants has lower abundance of *Faecalibacterium prausnitzii*, while nutrient counseling over 3 month could increase quantity of *Faecalibacterium prausnitzii* and epigenetically upregulate GPR41 and long interspersed nuclear element 1 promoter activity [8]. Verdum et al. reported that increased abundance of *Faecalibacterium prausnitzii* in health subjects and revealed potential proinflammatory change in microbiota diversity in obese cluster [9]. Others study also showed a lower level of *Faecalibacterium prausnitzii* species in obese cases with T2DM is directly linked to chronic inflammation. Previously, oral administration of commensal bacterium *Faecalibacterium prausnitzii* markedly improved intestinal inflammation, partly attributed to its metabolites production that inhibited NF- κ B-mediated inflammatory cascade, and suggesting a potential probiotics in Crohn's disease treatment [28]. A research reported that *Faecalibacterium prausnitzii* supernatant exerted anti-inflammatory activity and improved intestinal barrier function, and was recently identified by Quévrain and colleagues that a 15 kDa protein in the culture supernatant may contributed to attenuate the severity of dinitrobenzene sulfonic acid-induced colitis in mice [29]. In addition, *Faecalibacterium prausnitzii* also shown different feature of modulating diabetes progression through butyrate induced regulatory pathway. Several cohort studies have confirmed the compositional changes in *Faecalibacterium prausnitzii* are greatly correlated with T2DM [30]. An instance, a significant inverse association between low count of *Faecalibacterium prausnitzii* and hemoglobin A1c (HbA1c) level founded in T2DM patients [31]. A therapeutic effect

of *Faecalibacterium prausnitzii* as a potent probiotic supplement has been proposed for preventing diabetes in mice model [31]. Another bacteria indicator of maintaining intestinal health, *Akkermansia muciniphila* is recently attracted great interest. *Akkermansia muciniphila* was first isolated in 2004 and characterized by its mucin-degrading and SCFAs-producing abilities. Notably, *Akkermansia muciniphila* also played a critical role in maintaining intestinal health and its depletion was founded to inversely associated with several gastrointestinal-related disorders and metabolic disease. The fecal concentration of *Akkermansia muciniphila* and was shown to reduced several fold in ulcerative colitis and Crohn's disease patients [32]. Also, in patients of appendicitis, the abundance of *Akkermansia muciniphila* was significant reduced. Karlsson et al. demonstrated that the level of *Akkermansia muciniphila*-like bacteria were lower in preschool children with overweight and obesity [33]. Compared to normal weight gain pregnant women, *Akkermansia muciniphila* numbers were lower in women with excessive weight gain [34]. Moreover, the probiotic potential of *Akkermansia muciniphila* was proposed and further investigated in rodent models. Colonization of *Akkermansia muciniphila* by oral supplementation normalized HFD-induced metabolic disorders such as endotoxemia, inflammation, and IR in obese and T2DM mice. Other studies conducted gnotobiotic mice model by colonizing 14 synthetic human intestinal bacteria species in fiber-free diet feed Swiss Webster mice, resulting in recovering intestinal community and colonic mucus barrier lesion [35]. Similarity, it was reported that participant with higher abundance of *Akkermansia muciniphila* exhibited great efficiencies in improving metabolic parameters, especially in fasting blood glucose value and body mass index [36]. Furthermore, a pili-like transmembrane protein named Amuc_1100 was identified from *Akkermansia*

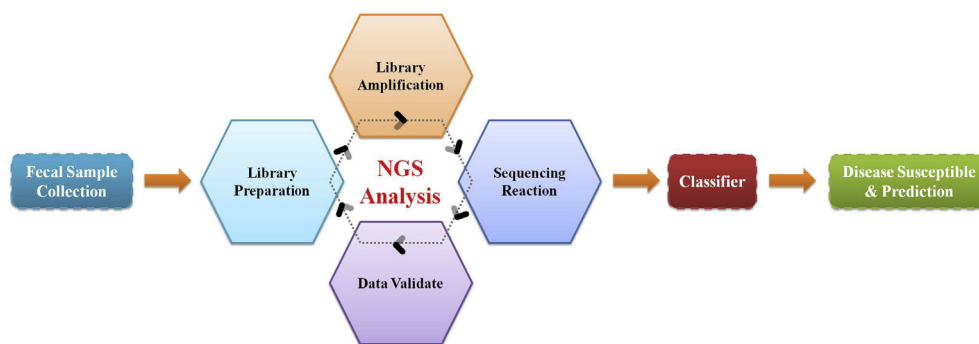


Fig. 2. Schematic representation of disease prediction flow chart. The flow chart caters to corresponding disease following a standardized protocol through next-generation sequencing (NGS) analysis, data extraction, and classification.

muciniphila, which is involved in benefiting immune function and intestinal mucosa integrity [37]. The aforementioned studies suggested that specific bacteria species, particularly of *Roseburia hominis*, *Faecalibacterium prausnitzii*, and *Akkermansia muciniphila* were referred to as next generation probiotics which could be served as a indicator and therapeutic tool for metabolic disease.

7. Novel predict tool for metabolic disease

With the fast grow in collecting healthcare records, big data analysis is expected to become popular in the future. Given that the term disease prediction is recently regard as a novel concept globally with major reason of it's application to prevent or forecast disease progression of human beings. The intestinal microbiota is recognized an essential metabolic organ response for dietary utilization and regulate host energy metabolism. It seem that referring to novel probiotic bacteria species, we have mentioned and a powerful analysis tool, next-generation sequencing (NGS) for big data construction that may suitable for extracting information and generating a disease prediction model (Fig. 2). To assess the linkage between diabetes and host gut microbiota dysbiosis, compositional and functional change of microbiota during sub-clinical state of diabetes was analysis in 36 fecal spacemen of Korea twin participants using metagenomic shogun sequencing technology. A next generation probiotic, *Akkermansia muciniphila* was indicated playing a crucial marker that precede disease onset, and functional alteration associated with low-grade inflammation in consist with previous observation [38]. These results suggested that *Akkermansia muciniphila* served as an early diagnostic biomarker of diabetes and applicable for microbial-based metabolic therapy. Although studies have suggested specific bacterial taxa might potentially used as a predictor/biomarker for the early diagnosis of MetS, global complexity of human intestinal microbiome and individual host properties limits the development of significant means for optimizing personal microbial-related references and disease model. To overcome the difficulty of intestinal microbiota complexity and diversity over country, ethnicity, and region, it still needs deeper and comprehensive studies to clarify the role of specific-species bacteria/novel potential probiotics in metabolic disease and determined a new disease risk algorithm or personalized based medicine. Emerging sequencing technology, high throughput analysis such as next-

generation sequencing and shotgun metagenomic methods enables generation of thousands or even millions of sequence reads from specimens and help profiling intestinal microbial diversity. The massive databases of phylogenetic and functional diversity have provided preliminary information of microbial communities between healthy and metabolic impairments. Global collaborative efforts such as International Census of Marine Microbes project and European Metagenomics of the Human Intestinal Trace project have provided preliminary microbial communities dataset and thus, necessitates methods to acquire meaningful data for multidimensional analysis [39]. Recently, machine learning methods exert great potential to process large data and applied to exploit microbial community datasets. Supervised machine learning algorithms such as support vector machine (SVM), random forest (RF), and gradient boosting (GB), can help developing multi-layer perceptrons, which might potentially applied to extract microbiome data [40]. Therefore, the consistently growing *in vivo* and *in vitro* investigations with metabolic associated diseases requires an emergency advance from interventional evaluation to predictive, preventive, and precision medicine. The flow chart caters to corresponding disease following a standardized protocol through NGS analysis, data extraction, and classification.

8. Conclusion

To date, the intestinal microbiota has been proven to greatly associate with host metabolic status and disease development. Modern sequencing technology has provided a fast and convenient way to identified specific alteration of the intestinal microbiota between disease and health. However, the present review summarized results from human clinical trials and animal studies, and gives a perspective of intestinal microbiota balance and diversity modulate metabolic diseases which emphasized the commercial development and clinical application. Although there is a substantial heterogeneity in microbial composition between species and needs further confirmed. Finally, we also proposed a disease predicted model in performance of NGS based detection and suggested the futurity of this proposed model.

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Conflict of interest

The authors declare that no conflicts of interest exist.

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