Gut Microbiota Dysbiosis and its Potential Application as Biomarker in Various Cancer

Introduction:

Human body comprises 'second genome' which is gut microbiome. The vast number of microorganisms that reside in the gut are collectively termed as 'gut microbiota'. Microorganisms like bacteria, archaea, fungi, eukarya represent the gut microbial population. The most widely present bacterial population is of *Bacteroidetes* and *Firmicutes*. *Proteobacteria, Actinobacteria, Verrucomicrobiota* are also a part of gut bacterial population (Thursby et al., 2017). An individual's gut microbiota composition keeps developing throughout the lifespan and many factors affect the composition of gut microflora. It starts changing from infancy and keeps changing through adulthood, pregnancy and then parturition. The development of gut starts as infants depending upon the mode of delivery, feeding types, any antibiotic exposure and environment, while the adult microbiome largely depends upon the diet, and lifestyle changes (Krakovski et al., 2022). Other factors like host genetics, stress, geographical location, mode of delivery, diet, any diseased condition, and treatment involving use of antibiotics can alter the healthy composition of gut microbiota (Darrien et al., 2019).

The gut microbiome performs various vital functions such as production of vitamins, metabolites, metabolism of dietary fibres, and systemic infiltration of gut pathogens. GM plays a vital role in maintaining all these functions and any imbalance in these equations may lead to impaired microbiome, a condition leading to dysbiosis, linking to many diseases including cancer.

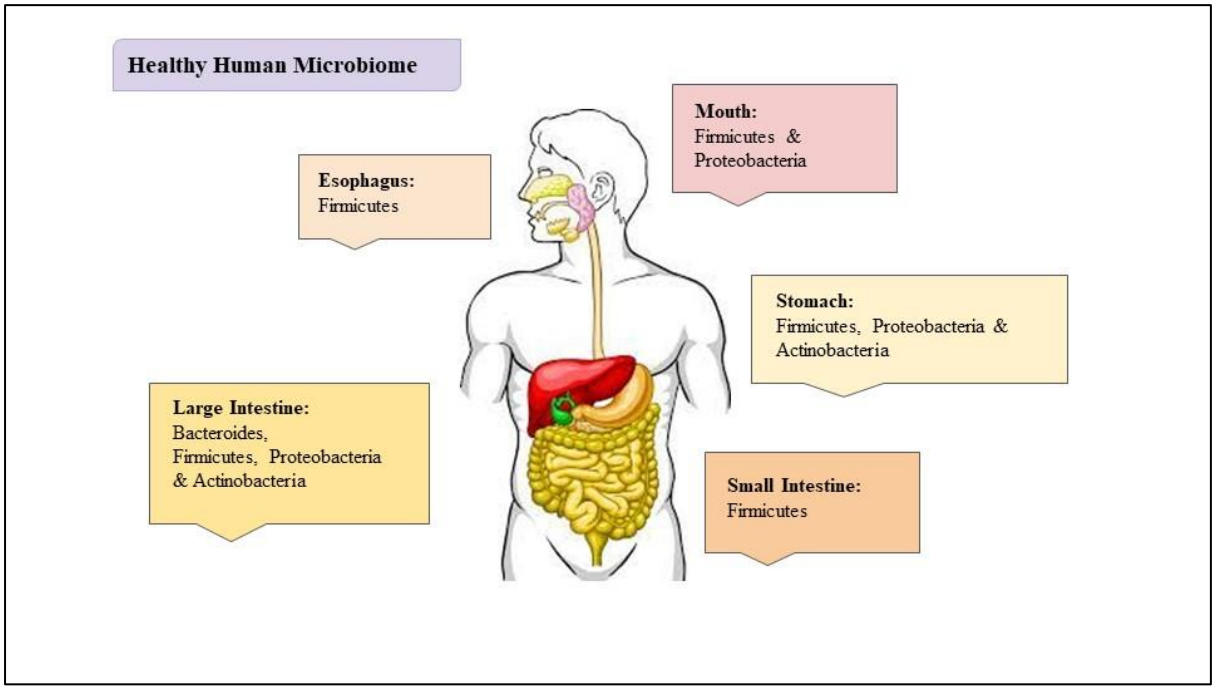

Fig.1: Healthy Human Microbiome

Gut dysbiosis is a condition within the gut which may contribute to pathogenesis at a particular site and even cause disease from bowel infiltration to neurodegenerative diseases and even cancer. During cancer, there are chances of gut dysbiosis and these dysbiosis can negatively

affect the host system, therefore triggering the tumor growth Almost 20% of tumorigenesis has been driven by microbial populations and large number of malignancies are associated with the gut imbalance and dysbiosis (Vivarelli et al., 2019).

As mentioned earlier, the human gut is an example of symbiotic relationship between bacteria, fungi, archaea, and protozoa. The ratio of microbes can vary from one individual to other and depend upon various lifestyle factors, diet, and nature. Gut microbiome and Cancer are the most researched topics in today's world. There have been rapid advances in human cancer research and gut microbiome, as the human gut can shape the microenvironment of host cells, which can either provide protection or promote cancer (Wu et al., 2020; Ağagündüz et al., 2023).

The gut microbiota is defined as the whole genome for any host gut microbiota which can encode more genes than any human genome. With an advancement in the field of metagenomics, bioinformatic analysis and the next generation sequencing tools, the whole genome sequencing of gut microbiota is possible via the analysis of 16s rRNA amplicons, to characterize the diversity of the gut. Host gut microbiota can either be tumor suppressive or oncogenic. There are various studies linked to pathogenesis of cancer due to gut microflora changes, leading to tumor progression, most common link has been identified for the gastro-intestinal cancers as well as the distal cancers which are connected to the gut (Vivarelli et al., 2019).

Gut Microbiota Dysbiosis and Cancer:

Brain Tumor:

The gut microbiota plays an important role in host maintaining metabolism, maturation, and regulation of several physiological process. The gut brain axis is the bidirectional communication between the gut and the central nervous system (CNS) that helps in multiple signalling pathways like entire nervous system, the sympathetic and parasympathetic nervous system, and the endocrine system.

Many evidence suggests the importance of gut microbiota and various cerebral diseases through gut-brain axis. There are evidences stating that the microbiome has a modulatory role in the central nervous system and its dysfunction (Krakowski et al., 2022). The metabolites produced by gut microflora and neurotransmitters can change the CNS microenvironment, immune system and the endocrine system. Studies have shown correlation regarding the gut dysbiosis and brain tumor that there are changes in microglial which can trigger a disruption of a humoral immune response in the brain tumor microenvironment (Li et al., 2022).

16s r-RNA gene amplicon sequencing study published in 2022 showed the gut microbiota alteration in patient with brain tumor and healthy controls. In patients with brain tumor, pathogenic bacterial population including *Fusobacteria* and *Proteobacteria* were present in an increased amount while the amount of beneficiary probiotics like *Bifidobacterium* and *Lachnospira* was reduced. This finding proposes that gut microflora may be used as a predictive and diagnostic marker for brain tumors.

GM and Lung Cancer:

According to GLOBOCAN 2020 data, lung cancer is the leading cause of death among various cancers globally (Sung et al., 2021). It usually begins in airways (bronchi or bronchioles) or in alveoli. Lung cancer is mainly classified in two categories: small lung cell cancer and non-small cell lung cancer (Lemjabbar-Alaoui et al., 2015). A research study published in the year 2018 highlighted the role of fecal microflora in lung cancer patients. Upon 16s r-RNA sequencing of lung cancer and healthy control groups, it was seen that in lung cancer group there was an overabundance of phyla *Bacteroidetes, Fusobacteria, Cyanobacteria, Spirochaetes* and *Lentisphaerae* with reduced levels of *Firmicutes* and *Verrucomicrobiota*. At genus level, there were higher levels of *Bacteroidetes, Veillonella* and *Fusobacterium* in lung cancer group along with lower levels of *Faecalibacterium, Enterobacter, Dialister, Escherichia-Shigella* and *Kluyvera*. This study shows that there is a reduction in the *F/B* ratio in lung cancer patients. This study also analysed the correlation between gut microbiota and inflammation related markers of lung cancer. It was seen that *Escherichi-Shigella* and *Enterobacter* were in positive correlation with serum NLR while *Dialister* was in negative correlation with NLR levels. *Dialister* was also seem to be in correlation with serum IL-12 levels and CTLA-4 (Zhang et al., 2018). It is important to note that this study did not exclude the effect of smoking on gut microbiota. Another study was published a few years later which showed the gut microbiota population in non-smoker lung cancer patients, which is discussed below.

In 2021, a research study was published from Kobe University that investigated the alteration in the gut microbiota in the specific population of female never-smoker lung adenocarcinoma patients. They analysed the effects of age, BMI, tumor size, performance status, EGFR mutation status, Tumor-Node-Metastasis (TNM) stage, T-category, N-category and M-category on gut microbiota population. Through 16s r-RNA gene sequencing, they found out that there was a significant correlation between tumor category (T-category) and tumor size with gut microbiota population. There was a positive correlation between *Faecalibacterium* with T-category and tumor-size while there was a negative correlation seen between the levels of *Fusicatenibacter* and *Bacteroidetes* with T and tumor size categories. In case of EGFR-mutation positive patients, there was significant increased levels of *Blautia* while EGFR-mutation negative patients had reduced levels of *Bifidobacterium* and *Faecalibacterium*. These changes in the gut microbiota in lung adenocarcinoma could be confirmed as potential biomarkers upon further large-scale research (Otoshi et al., 2022).

Another research study published from China focused on the dysbiotic population of gut microflora in lung cancer patients and healthy controls. The lung cancer patients had significant lower levels of *Actinobacteria* (phylum), *Actinobacteria* (class), *Bifidobacteriales* and *Coriobacteriales* (order), Bifidobacteriaceae and Coriobacteriaceae (family) along with significantly higher levels of Enterococaceae (family) with *Enterococcus* genus. These findings suggest the use of these microbiome alteration as diagnostic markers (Zhuang et al., 2019).

GM and Liquid Tumors:

Leukaemia is known as liquid tumor or blood cancer and is characterised by abnormal proliferation of white blood cells (Nix et al., 2019). Myeloid leukemia spreads quickly if not treated on time. There is a strong need to develop new and advanced strategies for its diagnosis and treatment. Acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL) and chronic lymphoblastic leukemia (CLL) are the four main types of leukemia. Among these four, AML is the most prevalent leukemia in adults. It is characterised by abnormal proliferation of myeloblasts, platelets and red blood cells (RBC) (Licht et al., 2005). And CML is characterised by Philadelphia chromosome which is a result of translocation between chromosome 9 and chromosome 22 (Kurzrock et al., 1991). A study published in the year 2021 highlighted the gut microflora population in case of AML and CML patients (Yu et al., 2021). Upon 16s r-RNA gene sequencing, they found that in both cases of AML and CML when compared to healthy controls, there was a significant increase in phylum *Actinobacteria, Acidobacteria* and *Chloroflexi* and genus *Streptococcus.* A significant decrease was seen in phylum *Tenericutes* with genus *Megamonas, Lachnospiraceae NC2004* and *Prevotella 9.* These significant results direct our attention to the role of dysbiotic population of gut microbiota in AML and CML patients. The approval of this study at large scale might be helpful to understand the role of gut microbiota as a biomarker for myeloid leukemia.

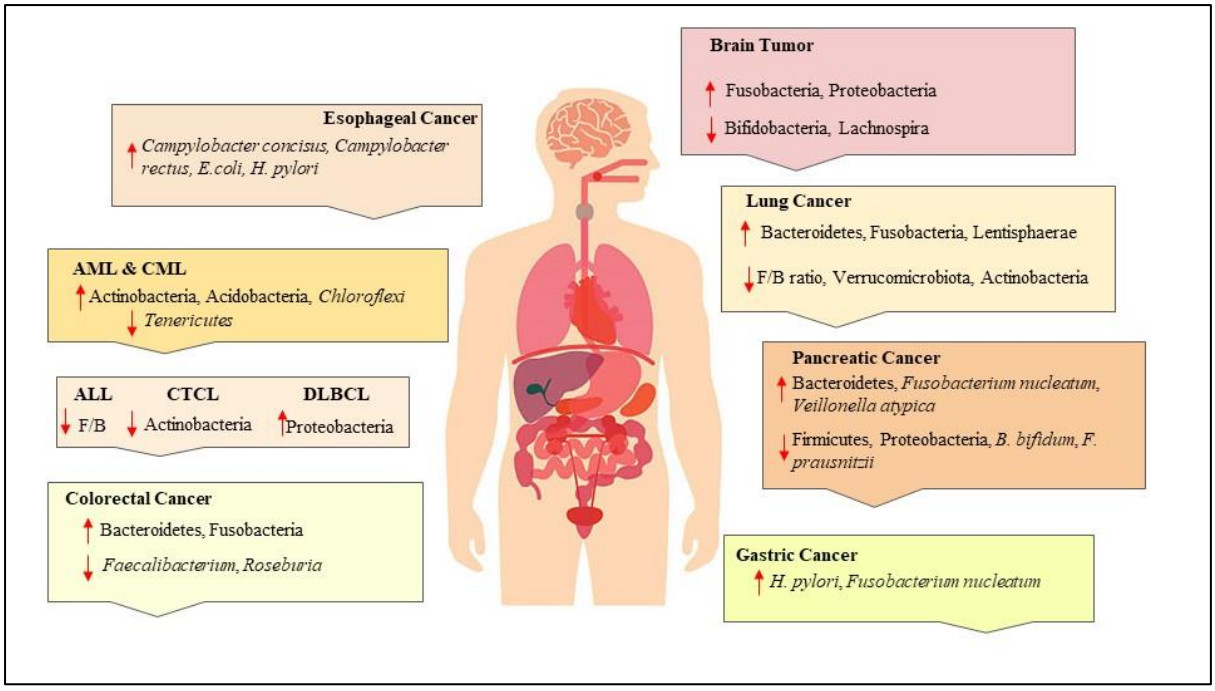

Fig-2: Potential Gut Microbiota Biomarkers in Various Cancers

Another study was published that showed the gut microbiota profiling in the paediatric patients with acute lymphoblastic leukemia (ALL) (Liu et al., 2020). This study found out the significant quantitative differences between ALL and healthy controls using 16s r-RNA quantitative microarray. It was seen that in ALL, *Bacteroidetes claurus* was present in higher levels than that in controls. While there was significant decrease in *Fusobacterium naviforme, Edwardsiella tarda and Roseburia faecis*. This study also supports the positive association between *Edwardsiella tarda and Prevotella* with interleukin-10 which is already been reported to be a prognostic marker for paediatric ALL (Lo et al., 2016; Kinderleben et al., 2005).

Rajgopala et al., in 2016 published a paper that involved the study of gut microbiota in pediatric and adult patients with ALL undergoing chemotherapy which were then compared with their healthy siblings. The 16s r-RNA sequencing showed an increased abundance of *Anaerostipes, Coprococcus, Roseburia* and *Ruminococus 2*. This indicates that in ALL patients, there is a significant decrease in *F/B* ratio which most certainly be used as microbial biomarker for childhood ALL patients (Rajagopala et al., 2016).

In 2017, another study came to surface that detected the change in the gut microfloral diversity in childhood ALL as well as ALL treated with antibiotics and were compared with antibiotic treated and untreated group (Bai et al., 2017). 16s r-RNA gene amplification revealed that ALL group had the lowest gut microbiota diversity which even decreased further when treated with antibiotics. It was also seen that there was dysbiosis caused by antibiotics as the *Firmicutes/Bacteroidetes* ratio was significantly decreased in the control group treated with antibiotics than untreated control group. In order to identify the bacterial taxa in ALL, they further compared the ALL and control group. Upon comparison of ALL and control group, the LDA scores of *Bacteriodales* and *Enterococcaceae* were high in ALL patients which indicates that these two species can be used as biomarkers for paediatric ALL.

Cutaneous T-cell lymphoma (CTCL) is an indolent Non-Hodgkin Lymphoma that initiates in cutaneous T-cells. Two subtypes of CTCL are mycosis fungoides (MF) and Sezary Syndrome (SS) which are considered as its advanced forms (Bobrowicz et al., 2020). In the year 2022, the first study was published in USA that characterised the gut microflora dysbiosis in CTCL (Hooper at al., 2022). They analysed the gut microbiota diversity of CTCL patients with their age-matched healthy controls through 16s r-RNA amplicon sequencing. It was seen that in CTCL patients, significant decrease was in seen in Actinobacteria at phylum level, Actinobacteria and Coriobacteriales at order level and *Anaerotruncus* at genus level. They also compared the gut microbiota population healthy controls and CTCL patients with advanced or higher form of disease. They found that in case of patients with advanced form that involves skin diseases had significantly lower levels of *Eggerthellaceae* and *Lactobacillaceae*. This study is one of its kind for CTCL case and it surely indicates the interlink between gut microbiota in CTCL and its progression and it should be taken under consideration.

Yuan et al., in 2021 published a study that provided the insights into the gut microbiota diversity in untreated diffuse large B-cell lymphoma (DLBCL) and healthy controls (Yuan et al., 2021). DLBCL is the most common type of non-Hodgkin Lymphoma that is aggressive and spreads quickly. It originates in germinal and activated B-cells and spreads to lymph nodes and then covers spleen, liver, bone marrow and other organs (Susanibar-Adaniya et al., 2021). They investigated the gut microbiota alteration through 16s r-RNA sequencing and it showed that DLBCL group had overabundance of phylum *Proteobacteria,* class *Gammaproteobacteria,* order *Enterobacteriales* and family *Enterobacteriaceae* when compared to healthy controls. DLBCL group also had a significant increase in the genus *Escherichia-Shigella, Enterococcus, Veillonella* and *Prevotella-2* with a significant decrease in the levels of *Lachnospira, Roseburiain* and *Allisonella.* And at species level, there was a significant increase in the levels of *E. coli* and *C. butyricum* along with lower levels of *B. fragilis* and *L. gravieae*. This study showed a consistent change in the abundance at all six

levels. Further study with multi-omics approach is required to confirm the use of these bacterial strains as a biomarker for DLBCL.

Gastrointestinal Tract Cancer:

The gut microbiome can vary from each person; the imbalance can cause disease, or it can be used as a powerful biological marker for detecting disease. Amongst the most mortal cancer types, gastrointestinal cancer accounts for one-third of the deaths by cancer (Arnold et al., 2020). These cancers can be triggered by infectious agents, chewing tobacco products, improper diet, lack of exercise, or energy imbalance The GI tract have large impact on metabolism, tissue development, and maintaining the homeostasis of the system and is considered the immune reservoir having the most immune cells (Wu et al., 2020; Ağagündüz et al., 2023).

Esophageal cancer is the sixth most common cancer in world. *Streptococcus viridans* reported as the most common oesophageal microbiota, while there is very less bacterial population. The transition of gram positive to gram negative bacteria in oesophagus, loss of bacterial diversity and atrophic gastritis can trigger an inflammatory response and leads to dysbiosis. Barret's oesophagus can be a rare type of cancer and they have a higher level of *Campylobacter concisus, Campylobacter rectus* and some *Escherichia coli* species. This cancer is the third most common cancer for death, caused by high salt consumption, smoked food intake, alcohol consumption, and *H. pylori* (the only known bacterial infection to date), regarded as carcinogens by IARC. The gastrointestinal tract (GI tract) starts from the oral cavity to the rectum, which involves many complex and dynamic microenvironments of bacterial populations, commonly called gut microbiome. The colon and distal gut, being part of the GI tract, have the largest ecosystem in our body, and it is a whole regarded as a metabolic organ producing many short-chain fatty acids (SCFAs) by soluble digestive fibres, which can regulate the homeostasis of the gut lining and its imbalance can be associated with disease such as obesity and diabetes (Wu et al., 2020).

Most commonly, the alteration in normal microflora can lead to cancer. For instance, an oral cavity bacterium, *Fusobacterium nucleatum,* can be a potential carcinogen for the colon when it interacts with *Peptostreptococcus spp. and Leptotrichia spp.*, which can activate the Wnt target genes, increasing the pro-inflammatory cytokines and evading the anti-cancer immune response. Thus, the intestinal flora could trigger the immune response and provide the possibility of cancer.

The increasing effect of imbalance in the gut can lead to dysbiosis and affect the immune system (Wu et al., 2020).

In the early 1990s, IACR classified *Helicobacter pylori* as a class I carcinogen for gastric cancer, the most common microbial infection related to cancer. The *H.pylori* infection occurs when the microflora is deficient in the normal microbiome, and the pathogens infect the gastric adenocarcinoma, with increasing tumor formation due to alterations in the physiological and microbial condition of the GI tract. The oncogenesis in gastric cancer by *H.pylori* infection is a three-step mechanism. The first step involves the release of cytokines such as VacA and CagA into the host cell, activating the oncogenic pathway. The second step involves the production of ROS species that activate the inflammasome pathways, causing atrophic gastritis. Finally, due to atrophic gastritis, parietal cells are destroyed, which upregulates gastric

acid production and activates oncogenic signals. Due to a reduced normal microbiome, there are chances of production of reduced nitrate, which can allow the formation of nitrites and carcinogenic N-nitroso compounds. (Wu et al., 2020; Ağagündüz et al., 2023)
Pancreatic cancer is the most malignant neoplasm among all cancers and by the time it is diagnosed, it had already been metastasized with severe aggressive form. Ren at al., in 2017 published the gut microbiota profiling of pancreatic carcinoma patients and healthy control groups. 16s r-RNA sequencing data revealed that pancreatic cancer patients had significantly increased proportions of phyla *Bacteroidetes* and significant reduction in the *Firmicutes* and *Proteobacteria.* While at genus levels, there were significantly higher levels of *Prevotella, Enterobacter, Hallela, Veillonella, Klebsiella* and *Selenomonas.* The remarkably reduced levels of *Bifidobacterium, Gemmiger, Blautia, Coprococcus, Flavinofractor, Clostridium IV, Dorea* and *Butyricoccus* were also seen. Pancreatic cancer patients had significant elevated levels of pathogens with lipopolysaccharides (LPS) producing bacteria and reduced levels of beneficial butyrate producing bacteria and probiotics. This study shed the light on altered gut microbiota population and its potential use as a non-invasive diagnostic marker in pancreatic cancer cases (Ren et al., 2017).

Another study published in 2022 showed the fecal microbiota profiling of patients with pancreatic ductal adenocarcinoma (PDAC), chronic pancreatitis (CP) and healthy control. PDAC patients had the lowest gut microbiota diversity with a predominant increase in *Veillonella atypica, Fusobacterium nucleatum/ hwasookii* and *Alloscardovia omnicolens.* While *Faecalibacterium prausnitzii, Bacteroidetes coprocola* and *Bifidobacterium bifidum* were present in reduced levels. This data suggests that these altered taxa can be considered as diagnostic markers for PDAC (Kartal et al., 2022).

GLOBOCAN 2020 data reports that colorectal cancer is the second most mortal cancer type worldwide (Sung et al., 2021). It is characterised by abnormal proliferation of rectal glandular epithelial cells. In the year 2015, a metagenomic analysis of fecal microflora in colorectal cancer (CRC) was published from China. They performed the metagenomic analysis of 74 CRC patients and 54 healthy controls and found the significant associations between CRC and *Fusobacterium nucleatum, Peptostreptococcus stomatis, Parvimonas micra* and *Solobacterium moorei.* This study also validated the findings of 20 gene markers from four ethnically different cohorts including France, Austria, Denmark, and China. These finding strongly indicates the universal profiling of gut microbiota in case of CRC. These findings can prove to be an efficient universal diagnostic marker for CRC. It is important to note here that this study did not exclusively publish the list of all 20 gene markers due to secrecy purposes (Yu et al., 2017).

Research study published in 2013 showed the altered fecal microflora alteration in CRC patients through 16s pyrosequencing and q-PCR (Wu et al., 2013). When the CRC group was compared with their healthy counterparts, there were significant elevation in the levels of *Bacteroidetes* and *Fusobacterium* species with a significant reduction in the abundance of *Faecalibacterium* and *Roseburia.* It was also seen that overabundance of *Bacteroidetes* is in correlation with the CRC stage. Additionally, two species which are considered to be potentially pathogenic including *Fusobacterium* and *Campylobacterium* were also seen in the

samples. These altered fecal microflora profiling with significant results indicates that in near future with extensive research at large scale, these can be confirmed to be used as potential diagnostic markers for CRC cases.

In the year 2017, Eklöf et al., published a nested-case study that focused on analysing the specific markers for *cIbA1*+ bacteria, afa-C+ diffusely adherent *E. coli* that foster the pks pathogenicity island and afa-1 operon respectively and *Fusobacterium nucleatum* in the stool samples. q-PCR results revealed that *F. nucleatum* was present in increased amounts in CRC patients than that in control. And markers for *cIbA1*+ bacteria along with afa-C+ diffusely adherent *E. coli* were also present in increased levels in the stool samples of CRC patients than in healthy controls. These findings suggest that presence of these biomarkers in stool samples can be utilised as a non-invasive diagnostics marker in case of CRC (Eklöf et al., 2017).

Conclusion and Future Prospects:

With recent advances in machine learning and bioinformatics techniques, gut microbiota research is taking a lead. The 'super organ' of the human body is crucial in maintaining one's health and any compositional or functional change of gut microflora which is termed as 'gut microbiota dysbiosis' could lead to a vast variety of pathological conditions. Number of studies have illustrated the role of gut microbiota and its dysbiosis in various types of cancer like CRC, lung cancer, leukemia, lymphoma, brain tumors, GIT-tumors, etc. The significant results from all those studies draws our attention to the use of gut microflora as diagnostics or prognostic markers. Alternative treatment strategies can also be designed to balance the dysbiotic population of gut microbiota in specific cancer type. Despite of numerous studies available, there is a strong need to conduct the large-scale studies to ultimately confirm the already reported studies. Most of these reported studies call for the need of large-scale research for further validation. Apart from this, a multi-omics approach involving different cohorts with different age groups would also aid in precise identification of gut microbial population. Designing an algorithm to eliminate the overlap of markers for different diseases is also required. Undoubtedly, the association between gut microflora dysbiosis, carcinogenesis and cancer progression exist, however the question of 'how' it is involved in the scenario remains as it is. Continuous efforts in clinical and preclinical trials for sequencing the gut microflora profile in patients would be helpful to create a clear link between dysbiotic gut microfloral population and its use as biomarker in cancer cases. Accounting these challenges and opportunities will bring the new era for development for microbial diagnostics and prognostic markers.

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