mainly from the phyla Firmicutes (30%-50%), Bacteroidetes (20%-40%), followed by Actinobacteria and Verrucomicrobia. is complex, diverse and dynamic communities of microbiota are known to play a signi cant role in health. e microbiota participates in digestion and extraction of nutrients, protection against infection, in the host immune response, drugs metabolism and is also involved in regulation of host metabolism [14]. We can divide the microbiota in mucosa-associated and luminal ora, whether the microbes penetrate the mucosal layer or are located in the lumen [15]. e luminal bacteria are less abundant than the mucosa-associated bacteria [16]. Furthermore, when comparing microbiome from stool and mucosal tissue samples, di erent populations are found [17]. e colonic mucosal communities are adherent to surface-associated polysaccharide matrices and are therefore less a ected by hydrodynamic shear forces. ese communities rooted to the mucosa interact with the immune system and appear to be more relevant to diseases such as CRC.

## Methods

For this review, a literature search was performed using the PubMed database. e search key terms were ("microbiome" or "microbiota" or "intestinal ora") and ("colorectal" or "colon" or "rectal" or "rectum") and ("cancer" or "neoplasm" or "neoplasia"). Only articles published in English and during the period of January 2013 to June 2016 were selected. e articles of the initial search have been screened for their potential eligibility according to the content of the title and/or abstract.

**Citation:** Lopes V, Faria G (2018) Beyond Microbiota and Colorectal Cancer: A Critical Review. J Oncol Res Treat 3: 120.

Page 4 of 7

Harnold et al proposed a bacterial counterpart of the genetic

**Citation:** Lopes V, Faria G (2018) Beyond Microbiota and Colorectal Cancer: A Critical Review. J Oncol Res Treat 3: 120.

Page 5 of 7

Ohigashi et al detected lower concentrations of short chain fatty acids in feces of CRC individuals, and an associated increase in pH. More precisely, three types of organic acids (acetic acid, propionic acid and butyric acid), usually the most abundant in the gut, were reduced [37]. Short chain fatty acids are important nal products of bacterial carbohydrate fermentation in the gut. Butyrate in particular is thought to be important in maintenance of a healthy intestinal environment. It's considered to be the preferred energy substrate for the colonocytes, and apparently stimulates a physiologic pattern of cell proliferation and suppresses tumor cells proliferation in the colonic crypts. It also participates in the maintenance of intestinal acidity, prevention of toxin absorption and promotion of cancer apoptosis [38]. According to Hold et al, some of the main butyrate-producing bacteria are Roseburia intestinalis, Faecalibacterium prausnitzii and Eubacterium hallii [39]. In Tables 1 and 2 we can see that Faecalibacterium and Roseburia were found diminished in CRC/adenoma cases in some studies. In adenoma cases, fecal short chain fatty acids and pH were intermediate between normal individuals and CRC cases, and there were no di erences detected between di erent CRC stages. is suggests that these variations are not consequent to the cancer itself [40] Baxter et al. found a negative correlation between the number of tumors and butyrate production capacity. It was also found a positive correlation between tumor count and mucin degradation. Disruption of the mucosal barrier integrity by mucin degradation could possibly lead to increased in ammation in Figure 2. ese are some of the main mechanisms that are thought to take part in promotion of carcinogenesis by bacterial populations. However, there's a much wider range of possible interactions and mechanisms studied and a lot of questions to answer.

### Beneficial roles of bacteria

Many authors hypothesized that certain bacteria may have a role in protection against pathogens and possibly prevent the progression of cancer. Feng et al observed that some of the control-enriched species were lactic acid-producing bacteria Bifidobacterium animalis, Streptococcus mutans and S. thermophilus. Lactic acid participates in gut acidi cation and inhibits intestinal amino acid degradation. It was also reported to accelerate colon epithelial cell turnover in mice. ere is evidence that advanced colorectal adenoma or carcinoma patients are deficient in lactic acid-producing commensals such as Bifidobacterium, that could potentiate daily epithelial renewal and inhibit potential pathogens [41]. Lactococcus also a lactic acid-producing bacteria, were over-represented in CRC patients besides playing a probiotic role in colon. Short chain fatty acids are important microbial metabolites and butyrate has been shown to have substantial anti-tumorigenic properties [42]. Butyrate is thought to be important in the maintenance of a healthy intestinal environment, participating in several bene c and antitumoral processes. Some of the main butyrate-producing bacteria (Roseburia intestinalis, Faecalibacterium prausnitzii) were found diminished in CRC/adenoma cases in some studies. is loss of short chain fatty acids producing bacteria populations is likely to play a synergistic role in potentiating tumorigenesis [43]. Lactobacillus spp. interacts with the host by binding to human mucus and they are currently used as probiotics. It is not yet understood if the e ect is direct (through immune modulation, for example) or indirect (via alteration of the intestinal microbiota) [44].

### Clinical Relevance

Zackular et al. identi ed a panel of bacterial populations that could indicate both the progression from healthy tissue to adenoma and the progression from adenoma to carcinoma, and created a screening model combining BMI, FOBT, and the microbiome data. is model provided excellent discriminatory ability. ey also compared the microbiome test with the FOBT, and assessed that the likelihood ratio of a positive FOBT was lower than the likelihood ratio of a positive microbiome test. For better understanding, they explained that for a 65 years old person with a positive FOBT, there was a 1 in 15 chance of having an adenoma. is contrasts with 1 in 9 chances using a positive microbiome test in the same 65-year old. It was concluded that the sensitivity of the microbiome test was greater than the sensitivity of the FOBT [45].

George Zeller et al. used metagenomics to explore microbiota potential for CRC detection, hypothesizing that a combination of marker species could be used to improve screening. ey selected the four most discriminative species, (two *Fusobacterium* species, *Porphyromonas asaccharolytica* and *Peptostreptococcus stomatis*) enriched in CRC patients. is metagenomic classi er proved to be slightly better than FOBT. ey also combined the two tests and obtained sensitivity 45% higher than FOBT alone. e authors then assessed for external validation, applying the classi er in cohorts from di erent countries. ey concluded that high accuracy detection was still possible even with cohort di erences. It was also concluded this classi er has potential for early detection, since the sensitivity was similar for early-stage and late-stage CRC. ese markers were also tested in IBD patients, and the most discriminative markers were all signi cantly higher in CRC, proving its speci city for CRC (29). e future application of these markers in population screening relies on the development of cost-e ective methods. With this in mind, Zeller et al tested an alternative 16S sequencing classi er for CRC, and it accomplished almost as good an accuracy as the metagenomic model [46]. A recent study tested the e ect of probiotic Lactobacillus salivarius REN

**Citation:** Lopes V, Faria G (2018) Beyond Microbiota and Colorectal Cancer: A Critical Review. J Oncol Res Treat 3: 120.

Page 7 of 7

27. Zhu Q, Jin Z, Wu W, Gao R, Guo B, et al. (2014) Analysis of the intestinal lumen microbiota in an animal model of colorectal cancer. PLoS One 9: e90849.

28. Tjalsma H, Boleij A, Marchesi JR, Dutilh BE (2012) A bacterial driver-passenger model for colorectal cancer: beyond the usual suspects. Nat Rev Microbiol 10: 575-582.

29. Zeller G, Tap J, Voigt AY, Sunagawa S, Kultima JR, et al. (2014) Potential of fecal microbiota for early-stage detection of colorectal cancer. Mol Syst Biol 10: 766.

30. Ohigashi S, Sudo K, Kobayashi D, Takahashi O, Takahashi T, et al. (2013) Changes of the intestinal microbiota, short chain fatty acids, and fecal pH in patients with colorectal cancer. Dig Dis Sci 58: 1717-1726.

31. Scheppach W, Weiler F (2004) the butyrate story: old wine in new bottles? Curr Opin Clin Nutr Metab Care 7: 563-567.

32. Scheppach W (1994) Effects of short chain fatty acids on gut morphology and function Gut 35: S35-S38.

33. Hold GL, Schwiertz A, Aminov RI, Blaut M, Flint HJ (2003) Oligonucleotide probes that detect quantitatively significant groups of butyrate-producing bacteria in human feces. Appl Environ Microbiol 69: 4320-4324.

34. Baxter NT, Zackular JP, Chen GY, Schloss PD (2014) Structure of the gut microbiome following colonization with human feces determines colonic tumor burden Microbiome 2: 20.

35. Feng Q, Liang S, Jia H, Stadlmayr A, Tang L, et al. (2015) Gut microbiome development along the colorectal adenoma-carcinoma sequence. Nat Commun 6: 6528.

36. Zackular JP, Rogers MA, Ruffn MTT, Schloss PD (2014) the human gut microbiome as a screening tool for colorectal cancer. Cancer Prev Res (Phila) 7: 1112-1121.

37. Fukugaiti MH, Ignacio A, Fernandes MR, Ribeiro Junior U, Nakano V, et al. (2015) High occurrence of Fusobacterium nucleatum and Clostridium diffcile in the intestinal microbiota of colorectal carcinoma patients. Braz J Microbiol 46: 1135-1140.

38. Wang R, Jiang L, Zhang M, Zhao L, Hao Y, et al. (2017) The Adhesion of Lactobacillus salivarius REN to a Human Intestinal Epithelial Cell Line Requires S-layer Proteins. Sci Rep 7: 44029.

39. Zhang M, Fan X, Fang B, Zhu C, Zhu J, et al. (2015) Effects of Lactobacillus salivarius Ren on cancer prevention and intestinal microbiota in 1, 2-dimethylhydrazine-induced rat model. J Microbiol 53: 398-405.

40. Chen ZF, Ai LY, Wang JL, Ren LL, Yu YN, et al. (2015) Probiotics Clostridium butyricum and Bacillus subtilis ameliorate intestinal tumorigenesis. Future Microbiol 10: 1433-1445.

41. Kumar A, Thotakura PL, Tiwary BK, Krishna R (2016) Target identifcation in Fusobacterium nucleatum by subtractive genomics approach and enrichment analysis of host-pathogen protein-protein interactions. BMC Microbiol 16: 84.

42. Yu YN, Yu TC, Zhao HJ, Sun TT, Chen HM, et al. (2015) Berberine may rescue Fusobacterium nucleatum-induced colorectal tumorigenesis by modulating the tumor microenvironment. Oncotarget 6: 32013-3226.

43. McCoy AN, Araujo-Perez F, Azcarate-Peril A, Yeh JJ, Sandler RS, et al. (2013) Fusobacterium is associated with colorectal adenomas. PLoS One 8,3ium]TJ-29.8 -2.01