British Journal of Cancer www.nature.com/bjc

EDITORIAL

Molecular Diagnostics

# Editorial on "A systematic review of microbial markers for risk prediction of colorectal neoplasia" by Yu and coauthors



Yu and colleagues show microbial markers are correlated with CRC and to a lesser degree with adenomas. Moreover, faecal microbial markers can be isolated from quantitative fecal immunochemical test cartridges and appear to improve results. If studies become less heterogeneous, it appears feasible to apply microbial markers in screening programmes.

*British Journal of Cancer* (2022) 126:1239–1240;
https://doi.org/10.1038/s41416-022-01774-x

Colorectal carcinoma (CRC) is the world's third most common cancer and the second leading cause of cancer death, being surpassed only by lung cancer [1]. Given this health burden, many countries have introduced screening programmes to increase early CRC detection. This is often done by performing a fecal occult blood test (FOBT) such as the quantitative fecal immunochemical test (qFIT), followed up by colonoscopy if needed. qFIT levels constitute a spectrum, with higher values correlating with increased chances of encountering malignancy upon endoscopy. Choosing a correct qFIT cut-off value is important in the context of population-wide screening. Choosing a lower cut-off value will increase the total number of adenomas and carcinomas found, but will also increase the number of colonoscopies performed in healthy individuals, putting them at risk of complications. This signifies the need for additional markers to improve the discriminatory ability of the qFIT.

Being preceded by the genome, epigenome, transcriptome, proteome, and metabolome, increasingly the microbiome is being recognised as a modifier of human disease. Most of the human microbiome is located in the gut, which contains about 400 different species of bacteria [2]. The number of microbial cells within the gut lumen is about 10 times larger than the number of eukaryotic cells in the human body [3]. These microbes are located mainly in the colon where living bacteria achieve concentrations of up to $10^{12}$ cells per gram of luminal contents [2]. This results in around 60% of faecal solids consisting out of bacteria [4]. Bacterial DNA can be successfully isolated from qFIT cartridges [5]. This makes it a test that could be added to currently implemented screening programmes.

In the current issue of the *British Journal of Cancer*, Yu and colleagues systematically review microbial markers for risk prediction of colorectal neoplasia [6]. Most of the studies included, i.e. forty-five, investigated the associations between colorectal neoplasia and fecal or oral microbial markers or serum antibody levels. An additional thirty included studies reported on prediction models containing microbial markers.

A central finding of the paper of Yu et al. is the extensive heterogeneity among included studies. This prohibited quantitative analysis. An attempt a reducing this heterogeneity would be highly valuable. Without it, reaching the level of evidence required for implementation of a microbial marker in addition to qFIT in a screening programme is far from reality [6].

Notwithstanding, descriptive syntheses showed one genus, i.e. *Fusobacterium* to be more abundant in both CRC and adenomas versus healthy controls, making it an interesting candidate marker. Several other species did show differences in abundance between CRC and healthy controls but this did not extend to adenoma patients versus healthy controls. *Fusobacterium* was also associated with metastasis and with poor survival outcomes in CRC patients.

With regard to the prediction models, the area under the curve of models discriminating between controls and patients with adenomas were lower compared to those discriminating between controls and CRC patients. Models using multiple bacterial species had relatively better performance. Additionally, on average, faecal microbial markers were shown to strengthen the accuracy of qFIT and improved the sensitivity and specificity of CRC prediction.

The most promising model was published by Guo and coauthors. A *Fusobacterium*, *Faecalibacterium*, and *Bifidobacterium* panel applied to 215 CRC patients and 156 controls achieved an AUROC of 0.94, when validated on a population of 152 CRC patients and 102 controls the AUROC found was 0.96. The best model discerning adenoma patients from healthy controls had an AUROC of 0.67, although combining it with qFIT improved it to 0.76 [5].

There is a need for a standardised protocol to perform studies such as those reviewed by Yu et al. In future studies clinical characteristics should be systematically described and individual patient data should be made available. This is how we could learn if the abundance of microbial markers is indeed specific for adenoma and CRC patients or merely associated with clinical characteristics associated with these conditions. If these markers prove to be independent variables, combining them with qFIT and clinical characteristics such as age and sex could lead to a significantly increased efficiency in CRC screening programmes. This could be directed to increasing the detection rate or to reducing cost. The latter would make nationwide screening programmes for CRC more attainable for middle income countries.

Apart from clinical applicability of these markers, one wonders whether the abundance of microbiota leads to the adenoma to carcinoma cascade or whether the presence of (pre)malignant lesions changes the abundance of certain genera. If the microbial

Received: 24 January 2022 Revised: 4 February 2022 Accepted: 22 February 2022
Published online: 15 March 2022

composition is a driving force of malignant degeneration, manipulations of the microbiome could become a cornerstone preventative health intervention. Lifestyle, diet interventions or pro- and antibiotic regimens could be employed to achieve a favourable microbiome.

It is evident from the systematic review published by Yu and colleagues in the current issue of the *British Journal of Cancer* that microbial markers, especially the genus *Fusobacterium*, are interesting candidate markers for CRC and to a lesser degree adenomas. As the faecal microbial markers were shown to strengthen the sensitivity and specificity of the qFIT, clinical application is feasible. This could lead to increased detection rates or reduced costs of screening programmes.

Maikel P. Peppelenbosch[1]✉ and Vincent T. Janmaat[1]
[1]*Department of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, The Netherlands.*
✉*email: m.peppelenbosch@erasmusmc.nl*

## REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin. 2022;72:7–33.
2. Simon GL, Gorbach SL. Intestinal flora in health and disease. Gastroenterology 1984;86:174–93.
3. Bengmark S. Ecological control of the gastrointestinal tract. The role of probiotic flora. Gut. 1998;42:2–7.
4. Stephen AM, Cummings JH. The microbial contribution to human faecal mass. J Med Microbiol. 1980;13:45–56.
5. Baxter NT, MTt Ruffin, Rogers MA, Schloss PD. Microbiota-based model improves the sensitivity of fecal immunochemical test for detecting colonic lesions. Genome Med. 2016;8:37.
6. Yu L, Zhao G, Wang L, Sun J, Li X, Zhu Y, et al. A systematic review of microbial markers for risk prediction of colorectal neoplasia. Br J Cancer. 2022.

## AUTHOR CONTRIBUTIONS

MP and VJ conceived and designed the work that led to the submission. MP and VJ drafted and revised the manuscript. MP and VJ approved the final version. MP and VJ agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## COMPETING INTERESTS

The authors declare no competing interests.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

## CONSENT TO PUBLISH

Not applicable.

## ADDITIONAL INFORMATION

**Correspondence** and requests for materials should be addressed to Maikel P. Peppelenbosch.

**Reprints and permission information** is available at http://www.nature.com/reprints

**Publisher's note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.