Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Correspondence

Returning to endoscopy normality through the support of a new non-invasive faecal test based on microbial signatures

Dear Editor,

During the height of the coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), many healthcare facilities needed to focus on screening for and treating patients with known or suspected COVID-19 [1]. This resulted in the diversion of healthcare workers and resources leading to the stop of colorectal cancer (CRC) primary screening and an alarming reduction in endoscopy activity during the COVID-19 pandemic, affecting and changing the daily practice of gastrointestinal endoscopy (both diagnostic and therapeutic) and will do so for the foreseeable future.

Altogether, this situation leads to pent-up demand for colonoscopy and translates into an oversaturation of limited endoscopic capacity, prompting further diagnostic and therapeutic delays of advanced neoplasia or early-stage malignancies [2]. In this sense, we paid much attention to the interesting article written by Buscarini *et al.* on the *Changes in digestive cancer diagnosis during the SARS-CoV-2 pandemic in Italy: A nationwide survey* [3] focused on the significant decrease in digestive cancers diagnosis because of the pandemic. Compared to 2019, in 2020 a reduction of 11.9% in the total of diagnoses of CRC was observed, followed by a 12.0% increase in mortality for delays beyond 12 months [3]. Similarly, in the USA a recent study reported a 50.0% reduction in CRC diagnosis as a result of the pandemic [4].

Clear and thoughtful policies regarding the timely restart of primary CRC screening programmes and how to prioritize patients in urgent need for subsequent colonoscopy evaluation are required. Currently, one of the technologies used for the screening of patients with symptoms compatible with CRC is the faecal immunochemical test (FIT). This strategy is usually used as a scoring system for prioritizing which patients should be promptly evaluated with colonoscopy establishing fast-tracking cancer referrals [5]. In some countries, colonoscopy is used as the second step in the screening process after testing positive in FIT even though the presence of blood in faeces can be due to pathological disorders other than neoplasia [6]. As stated by Buscarini *et al.* the COVID-19 pandemic has caused a significant disruption in colon cancer screening programmes in Italy, including a complete suspension of first (FIT) and second (colonoscopies) levels in some areas [3], data that can be extrapolated to the symptomatic population worldwide.

The National Institute for Health and Care Excellence (NICE) states that a cut-off of 10 µg of haemoglobin/g faeces should be used for symptomatic population [7]. The diagnostic accuracy following NICE Guidelines is 92.1% sensitivity for CRC and 62.9% for the detection of advanced neoplasia for symptomatic population with a high associated false-positive rate which leads to the performance of unnecessary colonoscopies [8]. The introduction of a new technology capable of reorganizing and prioritizing colonoscopies for diagnosis would allow to unblock the waiting lists caused by the COVID-19 pandemic. Recently, a non-invasive test based on faecal microbial signatures for the screening of patients with symptomatology compatible with CRC has been developed (Risk Assessment for Intestinal Disease – Colorectal Cancer, RAID-CRC) [6]. This test has been established taking the strengths of FIT and adding the extra value of highly specific bacterial signature for the detection of advanced colorectal neoplasia.

RAID-CRC combines 4 bacterial markers with FIT and it is aimed at increasing the specificity obtained by FIT alone and consequently reduce the number of false positive results that are translated to unnecessary colonoscopies [6]. The specific targeted bacterial markers are: *Peptostreptococcus stomatis* (PTST), *Bacteroides fragilis* (BCTF), *Bacteroides thetaiotaomicron* (BCTT), and Eubacteria (EUB) as the total bacterial load. Specifically, the algorithm of this stool DNA test consists of the combination of FIT with a cut-off of 10 µg of haemoglobin/g of faeces and the abundance ratios of the three bacterial markers (PTST/EUB, BCTF/EUB, and BCTT/EUB) [6].

In line with RAID-CRC results, our research group has analysed the diagnostic capacity of FIT at different cut-off points, comparing cut-offs of 16, 20, 24, and 31 µg of haemoglobin/g with 10, which has been used as the reference cut-off to calculate the reduction of false positive results (Table 1 and Table 2). For this study, 325 stool samples collected by patients with CRC related symptoms which referred for a diagnostic colonoscopy from primary and secondary health care of the Complexo Hospitalario de Ourense (Spain) were used. As detailed by Malagon *et al* [6], subjects were classified according to the diagnostic obtained in the colonoscopy in 4 groups: normal colonoscopy, non-advanced adenoma, advanced adenoma, and CRC. The FIT value was obtained from all patients. The diagnostic capacity of the different tests was calculated taking into account the detection of advanced neoplasia (advanced adenoma and/or CRC) and only CRC detection excluding advanced adenoma in the analysis (N=295).

As shown in Table 1 and Table 2 the diagnostic test that led to the highest reduction of false positives (FP) compared to FIT10 was FIT31+RAID-CRC, which reduced it a 60.3%. However, it must be noticed that this combination had the lowest sensitivity value (72.7%) of all the assessed diagnostic tests because of leading to an increase in the patients classified as false negative.

The false positivity of FIT10 was significantly reduced when the bacterial signature was added to the analysis, achieving a reduction of 49.2% with the combination of FIT10+RAID-CRC. This phenomenon highlighted the potential of the bacterial signature to

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Table 1
True positives (TP), false positives (FP), true negatives (TN), false negatives (FN), sensitivity, specificity, positive and negative predictive values (PPV and NPV) for the detection of advanced neoplasia of the different diagnostic tests. FIT10 FP ↓ (%): Reduction of false positives with respect to FIT10; NA, not applicable.

	FIT10	FIT10+RAID-CRC	FIT16	FIT16+RAID-CRC	FIT20	FIT20+RAID-CRC	FIT24	FIT24+RAID-CRC	FIT31	FIT31+RAID-CRC
TP	70	62	65	57	65	58	63	57	60	56
FP	63	32	51	29	47	29	42	28	36	25
TN	185	216	197	219	201	219	206	220	212	223
FN	7	15	12	20	12	19	14	20	17	21
Sensitivity (%)	90.9	80.5	84.4	74.0	84.4	75.3	81.8	74.0	77.9	72.7
Specificity (%)	74.6	87.1	79.4	88.3	41.0	88.3	83.1	88.7	85.5	89.9
PPV (%)	52.6	66.0	56.0	66.3	58.0	66.7	60.0	67.1	62.5	69.1
NPV (%)	96.4	93.5	94.3	91.6	94.4	92.0	93.6	91.7	92.6	91.4
FIT10 FP ↓ (%)	NA	49.2	19.0	54.0	25.4	54.0	33.3	55.6	42.9	60.3

Table 2
True positives (TP), false positives (FP), true negatives (TN), false negatives (FN), sensitivity, specificity, positive and negative predictive values (PPV and NPV) for the detection of colorectal cancer of the different diagnostic tests. FIT10 FP ↓ (%): Reduction of false positives with respect to FIT10; NA, not applicable.

	FIT10	FIT10+RAID-CRC	FIT16	FIT16+RAID-CRC	FIT20	FIT20+RAID-CRC	FIT24	FIT24+RAID-CRC	FIT31	FIT31+RAID-CRC
TP	47	44	47	44	47	44	47	44	46	44
FP	63	32	51	29	47	29	42	28	36	25
TN	185	216	197	219	201	219	206	220	212	223
FN	0	3	0	3	0	3	0	3	1	3
Sensitivity (%)	100.0	93.6	100.0	93.6	100.0	93.6	100.0	93.6	97.9	93.6
Specificity (%)	74.6	87.1	79.4	88.3	81.0	88.3	83.1	88.7	85.5	89.9
PPV (%)	42.7	57.9	48.0	60.3	50.0	60.3	52.8	61.1	56.1	63.8
NPV (%)	100.0	98.6	100.0	98.6	100.0	98.6	100.0	98.7	99.5	98.7
FIT10 FP ↓ (%)	NA	49.2	19.0	54.0	25.4	54.0	33.3	55.6	42.9	60.3

be used as a detector of true negative subjects. The increase in the FIT cut-off reduced the false positivity rate of FIT10 (19.0% reduction for FIT16, 25.4% for FIT20, 33.3% for FIT24, and 42.9% for FIT31), which was always further decreased when RAID-CRC was added to the analysis (54.0% reduction for FIT16+RAID-CRC, 54.0% for FIT20+RAID-CRC, 55.6% for FIT24+RAID-CRC, and 60.3% for FIT31+RAID-CRC). It must be noted that the reduction of false positivity correlated with an increase of the specificity of the diagnosis test and was inversely proportional to the sensitivity value since there is an increase in false negative results given by a wrong classification of mainly the advanced adenomas.

In this scenario, two Catalan university hospitals (Hospital Clínic de Barcelona and Hospital Universitari de Bellvitge) are currently evaluating the implementation of this new strategy for CRC early detection in symptomatic patients. RAID-CRC test is recommended to patients presenting symptoms or clinical signs compatible with CRC, except those with previously detected adenomatous polyps or diagnosis in persons with family history of CRC or with genetic predisposition such as those with Lynch syndrome.

If the implementation study verifies RAID-CRC higher diagnostic capacity compared to FIT alone, colonoscopy would be the recommended test for follow-up investigation for all individuals that test positive with RAID-CRC. The implementation study would enable to stratify patients according to the RAID-CRC result into groups for urgent and less urgent endoscopy evaluation.

The backlog caused by the COVID-19 pandemic demands urgent policy interventions reversing the impact of delays in cancer diagnosis and, as a direct consequence, survival rates [5]. These are particularly fundamental for patients experiencing symptoms compatible with CRC and, therefore, a prioritization strategy must be established to identify the fastest patients with precancerous lesions combining the restrictions imposed by the pandemic. In this line, the use of RAID-CRC would save up to 30% of total colonoscopies, therefore, the combination of FIT with the faecal bacterial markers would be superior in terms of cost-effectiveness to the current strategies. In addition, using RAID-CRC may achieve in both developed and resource-deprived regions, where colonoscopy facilities are limited [6].

This pilot study has emerged as prioritization but, with promising results guarantying an increased negative predicting value in a second phase, it could be proposed that those who obtain a negative result could avoid colonoscopy. This way, the cost-effective symptomatic early detection system will reduce up to 30% colonoscopies without influencing the CRC survival rate.

The addition of the RAID-CRC analysis in the screening strategy could add an extra value to the advanced neoplasia detection to symptomatic individuals and in terms of FIT false positivity reduction. In the extraordinary moments that we are living, with the collapse of the waiting lists for colonoscopies and the need to prioritize them to detect possible malignancies in early stages, the use of the FIT combined with the RAID-CRC as a screening step would be extremely helpful.

Declaration of Competing Interest

Dr. Ramió-Pujol, Mrs. Oliver, and Dr. Malagón are employees from GoodGut, company who has received private and public funding. Dr. Ramió-Pujol, Ms. Oliver, and Dr. Malagón report grants from MINECO and from CDTI, during the conduct of the study. Dr. Ramió-Pujol and Dr. Malagón have a licensed patent to GoodGut: PCT/EP2020/056575. Dr. Balaguer received an honorarium for consultancy from Sysmex, Cancer Prevention Pharmaceuticals, speaker's fees from Norgine, and editorial fee from Elsevier. The rest of the authors have nothing to disclose.

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