

## Performance value of high risk factors in colorectal cancer screening in China

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### Abstract

**AIM:** To analyze the performance value of high risk factors in population-based colorectal cancer (CRC) screening in China.

**METHODS:** We compared the performance value of the immunochemical fecal occult blood test (iFOBT) and other high risk factors questionnaire in a population sample of 13214 community residents who completed both the iFOBT and questionnaire investigation. Patients with either a positive iFOBT and/or questionnaire were regarded as a high risk population and those eligible were asked to undergo colonoscopy.

**RESULTS:** The iFOBT had the highest positive predictive value and negative predictive value in screening for advanced neoplasia. The iFOBT had the highest sensitivity, lowest number of extra false positive results associated with the detection of one extra abnormality for screening advanced neoplasias and adenomas. A history of chronic cholecystitis or cholecystectomy, chronic appendicitis or appendectomy, and chronic diarrhea also had a higher sensitivity than a history of adenomatous polyps in screening for advanced

neoplasias and adenomas. The sensitivity of a history of chronic cholecystitis or cholecystectomy was highest among the 10 high risk factors in screening for non-adenomatous polyps. A history of chronic appendicitis or appendectomy, chronic constipation, chronic diarrhea, mucous and bloody stool, CRC in first degree relatives, malignant tumor and a positive iFOBT also had higher sensitivities than a history of adenomas polyps in screening for non-adenomatous polyps. Except for a history of malignant tumor in screening for non-adenomatous polyps, the gain in sensitivity was associated with an increase in extra false positive results associated with the detection of one extra abnormality.

**CONCLUSION:** The iFOBT may be the best marker for screening for advanced neoplasias and adenomas. Some unique high risk factors may play an important role in CRC screening in China.

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**Key words:** Colorectal cancer; Cancer screening; Feces; Occult blood; Risk factors; Predictive value of tests

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### INTRODUCTION

The incidence of colorectal cancer (CRC) is increasing rapidly, and there is a similar incidence in some Asian populations to that in Western countries because of a more "Westernized" lifestyle and dietary habits<sup>[1]</sup>. A relatively long time for malignant transformation, together with improved survival associated with early detection of cancer, makes CRC an ideal target for screening. In source-limited Asian countries, the fecal occult blood test (FOBT) is the first choice for CRC screening because of its better population impact<sup>[1]</sup>. However, bleeding from cancers and precancerous polyps may be intermittent and

most small colorectal neoplasias do not tend to bleed<sup>[2]</sup>. Therefore, the immunochemical FOBT (iFOBT) alone inevitably misses some important lesions that do not bleed, or bleed intermittently. The iFOBT and a high risk factors questionnaire approach as primary screening followed by full colonoscopy examination as follow-up screening, has been recommended by the Department of Disease Control, the Ministry of Health of China as the protocol for population-based CRC screening in China<sup>[3]</sup>. However, the performance value of the iFOBT and a high risk factors questionnaire is still unknown in CRC screening practice in China. According to the definition of high risk factors by American Cancer Society<sup>[4]</sup>, individuals at higher risk for CRC include "individuals with a history of adenomatous polyps (HAP)". Therefore we used the data available in CRC screening practice in China to examine the performance value of each high risk factor using an acknowledged high risk factor - HAP - as a reference in CRC screening practice in China.

## MATERIALS AND METHODS

### *CRC screening protocol in China*

The CRC screening protocol of China has been published in a recent study<sup>[5]</sup>. Subjects (age should be defined as  $\geq 40$  years and  $\leq 74$  years) who have one or more of the following items are considered to be at high risk of CRC and should undergo colonoscopy: (1) Positive results from the iFOBT; (2) First-degree relatives with CRC; (3) A personal history of cancers or intestinal polyps; (4) 2 or more of the following items: (a) chronic diarrhea; (b) chronic constipation; (c) mucous and bloody stool; (d) history of appendicitis or appendectomy; (e) history of chronic cholecystitis or cholecystectomy; (f) history of psychiatric trauma (e.g. divorce, death of relatives).

### *Study population*

From July 2006 to December 2008, a screening program was implemented following the CRC screening protocol recommended by the Ministry of Health of China, for individuals aged 40-74 years in Xiacheng District, Hangzhou City, China. Among 33778 targeted residents, 16918 declined, 3646 participated only in the questionnaire investigation, and 13214 (39.1%) undertook both the iFOBT and questionnaire investigation.

### *Study design*

The 33778 subjects, aged 40-74 years, who lived in Xiacheng District were enrolled as the target population for our CRC screening practice. Therefore the targeted population can be classified into average, intermediate or high risk individuals. The targeted population was contacted by Chronic Disease Control (CDC) staff to explain the aim of the study, with an invitation to undergo both tests.

The aim of primary screening was to determine the high risk population among the targeted population by the iFOBT and questionnaire approach. Therefore the primary screening test kits included an iFOBT kit (Acon Biotech Co. Ltd., Hangzhou, China), a detailed instruction sheet, a consent form, and a questionnaire containing high

risk items. The iFOBT kit used is a qualitative method, with a hemoglobin detection threshold of 200 ng/mL. Participants were asked to prepare a fecal sample from 3 areas of a stool specimen. No specific dietary restriction was stipulated.

The study was approved by the local ethics committee and all participants gave written informed consent.

### *Identification of high risk subjects*

All participants learned how to use the iFOBT kit and how to fill in the questionnaire sheet under guidance of CDC staff. Feces samples were processed and results were obtained at the central laboratory of the local CDC. Processing and evaluation were not automated but were performed by trained staff and under strict quality control (double reading, control of frequency of positive tests, reproducibility). Scrutineers of the iFOBT were blinded to the subject's medical records. The screening procedure was considered positive when at least one of the tests was positive. All positive cases resulting from the primary screening were regarded as high risk subjects and those eligible were invited to the follow-up colonoscopy examinations. The CDC staff and primary care managers were responsible for inviting eligible high risk subjects for further colonoscopy examination.

### *Colonoscopy examination*

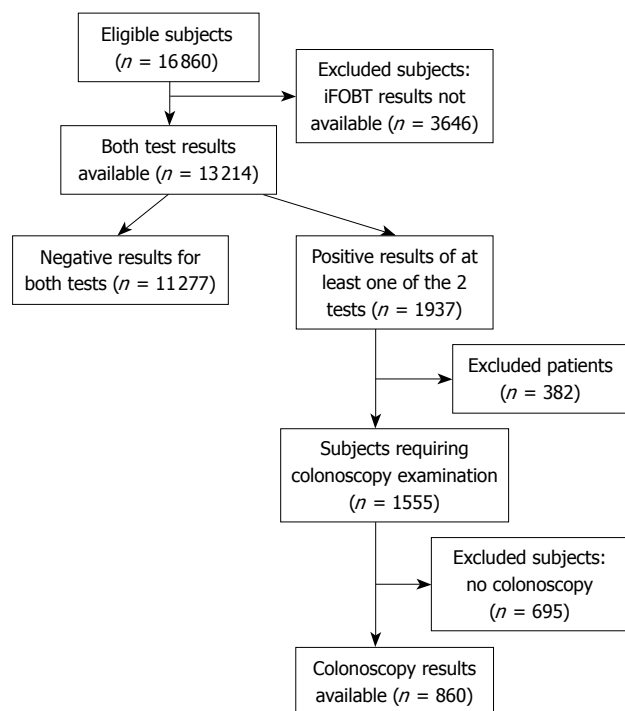
Colonoscopy examination was performed by gastroenterologists in endoscopy units of local hospitals and all participants gave written informed consent. The gastroenterologists recorded data using a standard form, including the quality of bowel preparation, the completeness of the colonoscopy, the number, size, and localization of any detected lesions, and the occurrence of complications. All polyps detected during the colonoscopy were immediately removed and/or biopsied for histologic diagnosis by pathologists. Those who were suspected of having CRC or had polyps that could not be removed endoscopically were referred for surgery. If a colonoscopy examination failed because of inadequate bowel preparation, inaccessibility of the cecum, or lack of satisfactory colonoscopy results, a subsequent colonoscopy would be performed within 1 mo.

### *Pathologic examination*

In subjects with more than one polyp, the most advanced pathological lesions or the largest lesion was included in the analysis. An advanced neoplasia was comprised of advanced adenomas (an adenoma measuring 10 mm or more in size, adenomas with high grade dysplasia, or an adenomas with villous component  $\geq 25\%$ ) and invasive cancer<sup>[6,7]</sup>. Non-adenomatous polyps included juvenile polyps, inflammatory polyps and hyperplastic polyps. Invasive cancer was defined as invasion by malignant cells through the muscularis mucosae. Intramucosal carcinoma and carcinoma *in situ* were categorized as high grade dysplasia. Pathologic slides of positive lesions were re-examined and diagnosed by consensus by pathologists.

### *Statistical analysis*

The population of participants in the primary screening



**Figure 1** Flow diagram of the study. iFOBT: Immunochemical fecal occult blood test.

comprised all patients who had given written consent ( $n = 16860$ ). Subjects who accepted only questionnaire investigation ( $n = 3646$ ) in the primary screening were excluded from the study. Subjects with at least one test positive ( $n = 1937$ ) were regarded as positive. A colonoscopy examination was not conducted in 382 subjects because of death, health problems, moving or other reasons. A further 695 subjects rejected a colonoscopy examination. Figure 1 provides a flow diagram of the study.

As the confirmatory procedure (colonoscopy examination) was restricted to subjects classified as positive in at least one of 2 tests (iFOBT and questionnaire examination) positive, the sensitivity of each high risk item could not be directly estimated. According to the theory originally suggested by Schatzkin *et al*<sup>[8]</sup>, we therefore compared the relative sensitivity (RSN) by calculating the ratio using HAP as reference. For example, if the number of true positive subjects for one high risk factor is denoted by  $m$  and the number of true positive subjects for HAP by  $n$ , RSN is calculated as  $m/n$ . Confidence intervals (95%) were calculated according to the formulae suggested by Cheng *et al*<sup>[9]</sup>. Using the theory recommended by Chock, the number of extra false positives associated with the detection of one extra true positive was denoted FP:TP, which was calculated as the ratio between the difference in the number of false positive subjects with one high risk factor versus HAP and the difference in the number of true positive subjects with one high risk factor versus HAP<sup>[10]</sup>.

## RESULTS

### Colonoscopic results of the iFOBT and questionnaire

A total of 21 CRC (2.4%) cases, 48 (5.6%) subjects with advanced adenomas, 147 (17%) subjects with adenomas,

**Table 1** Colonoscopy results of iFOBT and questionnaire  $n$  (%)

	Colorectal cancer	Advanced adenomas	Adenoma	Non-adenomatous polyps
iFOBT positive only	13 (61.9)	22 (45.8)	44 (29.9)	9 (16.7)
Both positive <sup>1</sup>	4 (19)	5 (10.4)	12 (8.2)	2 (3.6)
Only questionnaire positive	4 (19)	21 (43.8)	91 (61.9)	43 (79.7)
Total	21 (100)	48 (100)	147 (100)	54 (100)

<sup>1</sup>Both iFOBT and questionnaire positive. iFOBT: Immunochemical fecal occult blood test.

and 54 (6.3%) subjects with non-adenomatous polyps were detected in 860 colonoscopies. Table 1 shows colonoscopic results of the iFOBT and questionnaire. The iFOBT alone diagnosed 13 cases of cancer, 22 cases of advanced adenomas, 44 cases of adenomas, and 9 cases of non-adenomatous polyps while the questionnaire alone found 4 cases of CRC, 21 cases of advanced adenomas, 91 cases of adenomas, and 43 cases with non-adenomatous polyps. Four cases of CRC, 5 of advanced adenomas, 12 of adenomas, and 2 of non-adenomatous polyps were found in both positives. Table 2 shows the results of colonoscopy according to each high risk item. One perforation was recorded after colonoscopy (0.1%).

### The characteristics of the study population

Table 3 shows the characteristics of the study population. Of 13214 subjects who completed both the iFOBT and questionnaire investigation, 1937 had at least one positive test. The positive rate of the questionnaire investigation was markedly higher than that of the iFOBT (11.7% *vs* 3.6%). A colonoscopy examination was not conducted in 382 subjects (19.7%) because of death, health problems, or other reasons. A total of 860 (55.3%) subjects underwent colonoscopy. In subjects undergoing endoscopic examination, 60.3% were iFOBT positive only, 53.2% were questionnaire positive only, 64.9% were positive for both the iFOBT and questionnaire.

### Performance of high risk factors in screening for advanced neoplasia

Using HAP as the reference, the sensitivity of iFOBT was highest among all high risk factors. The sensitivities of history of chronic cholecystitis or cholecystectomy, chronic appendicitis or appendectomy, history of chronic diarrhea were also higher than that of HAP. The positive predictive value (PPV) and negative predictive value (NPV) of iFOBT were highest among all high risk factors for advanced neoplasias, but the gain in sensitivity was accompanied by an increase in FP:TP. The iFOBT had the lowest FP:TP ratio (Table 4).

### Performance comparison among high risk factors in screening for adenomas

Using HAP as standard, the sensitivity of iFOBT was also highest among 10 high risk factors. Higher sensitivities were also found in history of chronic appendicitis or appendectomy, chronic diarrhea, CRC in first degree relatives, and chronic cholecystitis or cholecystectomy. The

**Table 2** Colonoscopy results of high risk questionnaire items

	Cancer	Advanced adenomas	Adenomas	Non-adenomatous polyps	Normal results
iFOBT	17	27	56	11	128
History of malignant tumor	1	3	9	7	41
Colorectal cancer (CRC) in first degree relatives	2	7	29	11	81
History of adenomatous polyps (HAP)	0	9	25	6	48
History of mucous and bloody stool	5	4	15	10	101
History of chronic diarrhea	2	10	29	10	120
History of chronic constipation	0	8	24	13	102
History of chronic appendicitis or appendectomy	3	9	33	14	122
History of chronic cholecystitis or cholecystectomy	3	14	50	19	169
History of psychiatric trauma	4	5	18	2	73

**Table 3** Characteristics of the study population *n* (%)

	Subjects with 2 analyzable tests ( <i>n</i> = 13214)
Sex	
Male	5391 (40.8)
Female	7823 (59.2)
Age (yr)	
40-49	2711 (20.5)
50-59	4704 (35.6)
60-69	3683 (27.9)
70-74	2116 (16.0)
Positive items	
iFOBT	481 (3.6)
History of malignant tumor	172 (1.3)
CRC in first degree relatives	367 (2.8)
HAP	158 (1.2)
History of mucous and bloody stool	430 (3.3)
History of chronic diarrhea	709 (5.4)
History of chronic constipation	902 (6.8)
History of chronic appendicitis or appendectomy	1126 (8.5)
History of chronic cholecystitis or cholecystectomy	1538 (11.6)
History of psychiatric trauma	655 (5)

PPV of the iFOBT was 22.5%, just behind that of HAP (26%). The NPV of iFOBT was highest among all high risk factors. The gain in sensitivity was also accompanied by an increase in FP:TP ratio (Table 4).

### Performance comparison of high risk factors in screening for non-adenomatous polyps

Using HAP as standard, a history of chronic cholecystitis or cholecystectomy was the most sensitive marker in screening for non-adenomatous polyps. The sensitivities of other high risk factors except history of psychiatric trauma were also higher than that of HAP. The PPV of history of malignant tumor (10.6%) was highest among all high risk factors in screening for non-adenomatous polyps. Except for history of malignant tumor, the gain in sensitivity was accompanied by increase in the FP:TP ratio (Table 4).

## DISCUSSION

Colonoscopy is often regarded as the “gold standard” for detection of CRC<sup>[11,12]</sup>. Direct colonoscopy screening is the most accurate test for CRC. However because of its potential harm, acceptability<sup>[13]</sup>, availability, and expense<sup>[14]</sup>,

the use of colonoscopy as a one-step screening method for the whole targeted population is impractical in China. The use of noninvasive screening tests in primary screening, such as iFOBT and questionnaire investigation, have been adopted as the large scale population screening program in China<sup>[15]</sup>. The iFOBT and questionnaire investigation focused on different aspects. The iFOBT can detect bleeding lesions and the questionnaire can find lesions which do not bleed or bleed intermittently. Thus they may have different performance in screening colorectal abnormalities. To the best of our knowledge, the current study is the first analysis comparing the performance value of high risk factors in mass CRC screening in China. Because confirmatory examination was limited to subjects who had at least one positive test, studies calculated the RSN and relative false-positive rate in comparing the 2 screening methods<sup>[16,17]</sup>.

Colorectal adenomatous polyps are recognized as pre-cancerous lesions and are responsible for most cases of CRC<sup>[18]</sup>. Thus far, the important indicator for transition from adenomas to cancer has been the pathologic characteristics of the advanced adenomas. Thus it is important to find advanced adenomas and block the adenoma-carcinoma sequence in CRC screening. The iFOBT had the highest PPV, NPV and RSN, and the lowest FP:TP ratio in screening for advanced neoplasias, indicating that the iFOBT may be superior to other factors in screening for advanced neoplasias. Though some studies in Asian countries have shown that iFOBT is effective in CRC screening<sup>[19,20]</sup>, iFOBT alone may not be enough in CRC screening, because iFOBT inevitably misses some important lesions which do not bleed or bleed intermittently. A history of chronic cholecystitis or cholecystectomy, chronic appendicitis or appendectomy, and chronic diarrhea also had higher sensitivity than HAP, indicating that these unique Chinese high risk factors can detect a larger number of advanced neoplasias. Some studies have found an increase in the risk of CRC following cholecystectomy for gallstones<sup>[21-27]</sup>. Cholecystectomy also influences the adenoma to cancer transition, ultimately predisposing to the development of CRC<sup>[28]</sup>. A study from France supported the hypothesis that the appendix, as a lymphoid organ, plays a protective role in colon carcinogenesis<sup>[29]</sup>. These unique Chinese high risk factors for CRC may play an important role in screening for advanced neoplasias because of their higher sensitivity, which contributed to detection of a greater number of advanced neoplasias.



**Table 4** Comparison of the performance of high risk factors in screening advanced neoplasias, adenomas, non-adenomatous polyps using HAP as reference

	Advanced neoplasias				Adenomas				Non-adenomatous polyps			
	PPV (%)	NPV (%)	RSN	FP:TP	PPV (%)	NPV (%)	RSN	FP:TP	PPV (%)	NPV (%)	RSN	FP:TP
iFOBT	17.70	95.70	4.9 (2.42-9.87)	2.29 (1.36-3.83)	22.50	85.10	2.24 (1.4-3.52)	2.58 (1.37-4.87)	4.40	93	1.8 (0.71-4.58)	16 (3.39-75.58)
HMT	6.10	91.70	0.4 (0.17-1.19)		13.60	82.60	0.36 (0.18-0.7)		10.60	94	1.17 (0.39-3.48)	
FDR	5.70	91.30	1 (0.4-2.519)		18.50	83.20	1.16 (0.69-1.96)	8.25 (0.44-154.47)	7	93.90	1.8 (0.67-4.88)	6.6 (1.16-37.6)
HAP	9.40	92	1		26	84	1		6.30	93.70	1	
MBS	5.70	91.30	1 (0.42-2.39)		9.50	81.20	0.6 (0.33-1.08)		6.30	93.70	1.7 (0.66-4.38)	13.25 (2.02-86.77)
HCD	5.40	91	1.2 (0.54-2.63)	24 (1.87-307.35)	13.90	82	1.16 (0.72-1.88)	18 (1.1-293.1)	4.90	93.30	1.7 (0.71-4.08)	18 (3.2-101.33)
HCC	4.80	91	0.9 (0.35-2.33)		14.30	82.20	0.96 (0.56-1.65)		7.70	94.10	2.2 (0.88-5.49)	7.7 (2.26-26.21)
CAA	5.50	91	1.3 (0.59-2.83)	24.6 (1.63-370.18)	15.10	82.20	1.32 (0.8-2.16)	9.25 (1.52-55.7)	6.40	93.80	2.3 (0.88-5.99)	9.25 (2.96-28.79)
CCC	5.80	87.40	1.9 (0.87-4.12)	15.13 (4.47-51.23)	16.90	82.80	2 (1.26-3.16)	4.84 (2.43-9.65)	6.40	93.80	3.2 (1.38-7.42)	9.3 (4.5-19.22)
HPT	7.60	91.80	1 (0.42-2.39)		15.30	82.60	0.72 (0.43-1.2)		1.70	93	0.33 (0.07-1.63)	

HMT: History of malignant tumor; FDR: History of CRC in first degree relatives; MBS: History of mucous and bloody stool; HCD: History of chronic diarrhea; HCC: History of chronic constipation; CAA: History of chronic appendicitis or appendectomy; CCC: History of chronic cholecystitis or cholecystectomy; HPT: History of psychiatric trauma; PPV: Positive predictive value; NPV: Negative predictive value; RSN: Relative sensitivity; FP:TP ratio: The ratio between the difference in the number of false positive subjects with one high risk factor *vs* HAP and the difference in the number of true positive subjects with one high risk factor *vs* HAP. Values for RSN and FP:TP are mean (95% CI). RSN > 1: Sensitivity of the high risk factor is greater than that of HAP.

It would be unsafe to ignore adenomas < 10 mm because 30% of cancer is derived from 6-9 mm adenomas<sup>[30]</sup>. The questionnaire detected a greater number of adenomas than the iFOBT in our screening study. We also found that the iFOBT still had the highest sensitivity among all high risk factors, followed by history of chronic cholecystitis or cholecystectomy, chronic appendicitis or appendectomy, and chronic diarrhea. The iFOBT may also be superior to other factors in screening for adenomas because of high PPV and NPV, high RSN and low FP:TP ratio. Higher sensitivities indicated the important performance value of these unique Chinese high risk factors.

A history of chronic cholecystitis or cholecystectomy was the most sensitive marker in screening for non-adenomatous polyps, followed by history of chronic appendicitis or appendectomy, and chronic constipation. Though subjects with non-adenomatous polyps were not regarded as having increased risk of CRC, these polyps do not require surveillance colonoscopy, they may serve as a precursor to CRC in subjects with specific genetic and other molecular characteristics<sup>[31-34]</sup>. Thus it would be unsafe to ignore these polyps.

The study had several drawbacks. Firstly, to evaluate screening test performances among the general population, the ideal is to obtain sensitivity and specificity for all individuals. Because only eligible high risk subjects were invited and only about 55% of population accepted the colonoscopy examination, these results may not be completely representative of the general population. Secondly, although all the study population accepted both the iFOBT and questionnaire investigation, the colonoscopy uptake rate of the iFOBT positive only was

higher than that of the questionnaire positive only. This would slightly overestimate the RSN of the iFOBT.

HAP, an acknowledged high risk factor was used as the reference to calculate the relative ratio in this study. Therefore the other variables being compared may be underestimated. Even so, the iFOBT and some unique Chinese high risk factors - history of chronic cholecystitis or cholecystectomy, chronic appendicitis or appendectomy, and history of chronic diarrhea - still play an important role because of the higher sensitivities than that of HAP. The iFOBT may be superior to other factors in screening for advanced neoplasias and adenomas.

## ACKNOWLEDGMENTS

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## COMMENTS

### Background

The immunochemical fecal occult blood test (iFOBT) and high risk factors questionnaire approach as primary screening followed by full colonoscopy examination as follow-up screening, has been recommended as the colorectal cancer (CRC) screening guideline for population-based CRC screening in China. The performance value of the iFOBT and the high risk factors questionnaire is still unknown in CRC screening practice in China.

### Research frontiers

The limitation of the iFOBT is its low sensitivity for CRC. High risk factors for CRC among a Chinese natural population have been identified through a meta-analysis. The major advantage of the high risk factors questionnaire investigation is that it can detect lesions that do not bleed or bleed intermittently.

## Innovations and breakthroughs

This is believed to be the first study comparing the performance value of high risk factors in mass CRC screening in China. In this study, because participants with at least one positive factor were asked to undergo colonoscopy, the sensitivity of each high risk item could not be directly estimated. The authors therefore compared sensitivities by calculating the relative sensitivity using HAP (history of adenomatous polyps, an acknowledged high risk factor) as a reference.

## Applications

The study suggests that the iFOBT may be the best marker for screening advanced neoplasias and adenomas. Some unique Chinese high risk factors (history of chronic cholecystitis or cholecystectomy, chronic appendicitis or appendectomy, and history of chronic diarrhea) may play an important role in CRC screening in China because of higher sensitivities than that of HAP.

## Peer review

The authors have done much work in this study. The study is worthwhile and well performed.

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