

# Comparative Evaluation of Immunochemical Fecal Occult Blood Tests for Colorectal Adenoma Detection

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**Background:** Different immunochemical fecal occult blood tests (FOBTs) have been proposed for noninvasive colorectal cancer screening. Large-scale, colonoscopy-based screening studies that allow evaluation of these tests for the detection of precursor lesions are scarce.

**Objective:** To determine and compare performance characteristics of 6 qualitative immunochemical FOBTs for identifying colorectal adenomas among adults who attended screening colonoscopy examinations.

**Design:** Prospective screening study from January 2006 to December 2007.

**Setting:** 20 gastroenterology practices in Germany that did screening colonoscopy.

**Patients:** 1319 participants at average risk for colorectal neoplasia who were undergoing screening colonoscopy (mean age, 63 years; 50% men).

**Measurements:** 6 different qualitative immunochemical FOBTs were done with stool samples collected before bowel preparation for colonoscopy. Performance characteristics (sensitivity, specificity, predictive values, and likelihood ratios) of tests were measured by comparing test results with findings on colonoscopy. Technicians who read the tests were blinded to colonoscopy results, and colonoscopists were blinded to FOBT results.

**Results:** Overall, 405 participants (31%) had an adenoma and 130 participants (10%) had an advanced adenoma. Performance characteristics varied widely among tests. For the 2 best-performing tests (immoCARE-C [CAREdiagnostica, Voerde, Germany] and FOB advanced [ulti med, Ahrensburg, Germany]), the sensitivity for detection of advanced adenomas was 25% (95% CI, 18% to 34%) and 27% (CI, 20% to 35%), respectively; specificity was 97% (CI, 95% to 98%) and 93% (CI, 91% to 95%); and the positive likelihood ratio was 3.5 (CI, 2.2 to 5.4) and 2.5 (CI, 1.9 to 3.5).

**Limitation:** The study differed from real-life conditions in that stool samples were not directly dissolved in a buffer-filled vial; instead, a small container was used and stool was frozen before testing.

**Conclusion:** Qualitative immunochemical FOBTs could be an option for future colorectal cancer screening because they showed better performance characteristics for precursor lesions than guaiac-based FOBTs and are practical for mass screening. However, given the large differences in diagnostic performance among tests, careful evaluation of the different test variants is important.

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Colorectal cancer (CRC) is the third most common cancer in the world (1), with about 1 million new cases and more than 500 000 deaths per year. Because most cases of CRC are sporadic and develop from removable precancerous lesions (adenomas) and curable early-stage cancer (2), screening for CRC has high potential for reducing morbidity and mortality. Randomized, controlled trials have demonstrated reduced mortality with guaiac-based fecal occult blood testing (FOBT) followed by colonoscopy or sigmoidoscopy if the FOBT result is positive (3).

However, guaiac-based FOBT, which detects the pseudoperoxidase activity of heme or hemoglobin, has im-

portant limitations. It is not specific for human hemoglobin, and false-positive and false-negative results can result from certain compounds or medications in foods (for example, red meat or vitamin C) (4) that should be avoided during the days before testing. Another important limitation is the low diagnostic performance for precursors to CRC. An advantage of guaiac-based FOBT is the simple analysis, which can easily be done at the physician's office, even though reliable interpretation of test results requires training (5, 6).

Immunochemical FOBTs that use specific antibodies against human blood components overcome the problem of diet or medication restriction. Unlike quantitative immunochemical FOBTs, qualitative immunochemical FOBTs that mostly use immunochromatographic technology also allow simple, office-based analysis. However, there are differences among qualitative immunochemical FOBTs. For example, the antibodies used and the different detection limits may influence the diagnostic performance, especially with respect to detection of precursor lesions. We aimed to determine and compare performance characteristics of different qualitative immunochemical FOBTs for the detection of colorectal adenomas in a large sample of women and men undergoing screening colonoscopy.

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**METHODS****Study Design and Sample**

The analyses were part of the BliTz study (Begleitende Evaluierung innovativer Testverfahren zur Darmkrebsfrüherkennung), an ongoing screening study conducted in cooperation with 20 gastroenterology practices in southwestern Germany since January 2006 that aims to comparatively evaluate new tests for early detection of CRC. The study includes participants undergoing screening colonoscopy—a procedure that the German health care system has offered since October 2002 to average-risk persons 55 years or older. In Germany, preliminary consultation for any type of cancer screening is mostly done by general practitioners. For screening colonoscopy, patients are referred to the gastroenterologist only when the decision to have colonoscopy is made. All participants had a preliminary consultation with a gastroenterologist to receive detailed information and advice about screening colonoscopy. They were informed about and invited to participate in the study at that time.

After we received written informed consent, we asked patients scheduled for screening colonoscopy to provide a stool sample before bowel preparation. Physicians who did colonoscopy and histologic examination were blinded to FOBT results. After colonoscopy, we collected reports on colonoscopic and histologic findings and extracted information in a standardized manner while blinded to the results of stool testing. We did not query patients about adverse events of testing (such as psychological distress). The ethics committee of the University of Heidelberg, Heidelberg, Germany, approved the study.

We included patients who provided stool samples for qualitative immunochemical FOBTs until 13 December 2007. The **Figure** shows the numbers of all potentially eligible patients.

Of 1785 patients undergoing screening colonoscopy who agreed to participate, 111 were excluded because of visible rectal bleeding or preceding positive FOBT result. We excluded 13 patients because of inflammatory bowel disease. These patients usually receive close colonoscopic surveillance and would not be regarded as the target population for primary FOBT screening. We excluded 117 patients because they had undergone colonoscopy in the past 5 years and thus would not be eligible for primary FOBT screening (if the previous colonoscopy result was positive, they are recommended for colonoscopic surveillance; if the result was negative, they are at very low risk for colorectal neoplasia). We further excluded participants whose stool samples were collected after colonoscopy only (and thus violated the study protocol [ $n = 65$ ]), those with inadequate bowel preparation before colonoscopy ( $n = 79$ ), and those with incomplete colonoscopy (that is, the cecum was not reached, [ $n = 22$ ]). We excluded patients who received a histologically confirmed diagnosis of CRC (this subgroup comprised only 11 participants by the end

**Context**

Several immunochemical fecal occult blood tests (FOBTs) that use different antibodies against human blood components are available.

**Contribution**

This study compared characteristics of 6 qualitative immunochemical FOBTs and 1 guaiac-based FOBT to identify adenomas among adults who attended screening colonoscopy. The FOBTs had widely varying performance characteristics. Sensitivity and specificity for detecting advanced adenomas ranged from 25% to 72% and 70% to 97%, respectively, for the immunochemical tests and were 9% and 96%, respectively, for the guaiac test.

**Caution**

One-day stool samples were used, and stool was frozen before testing.

**Implication**

Qualitative immunochemical FOBTs have varying performance characteristics for detecting precancerous colorectal lesions.

—The Editors

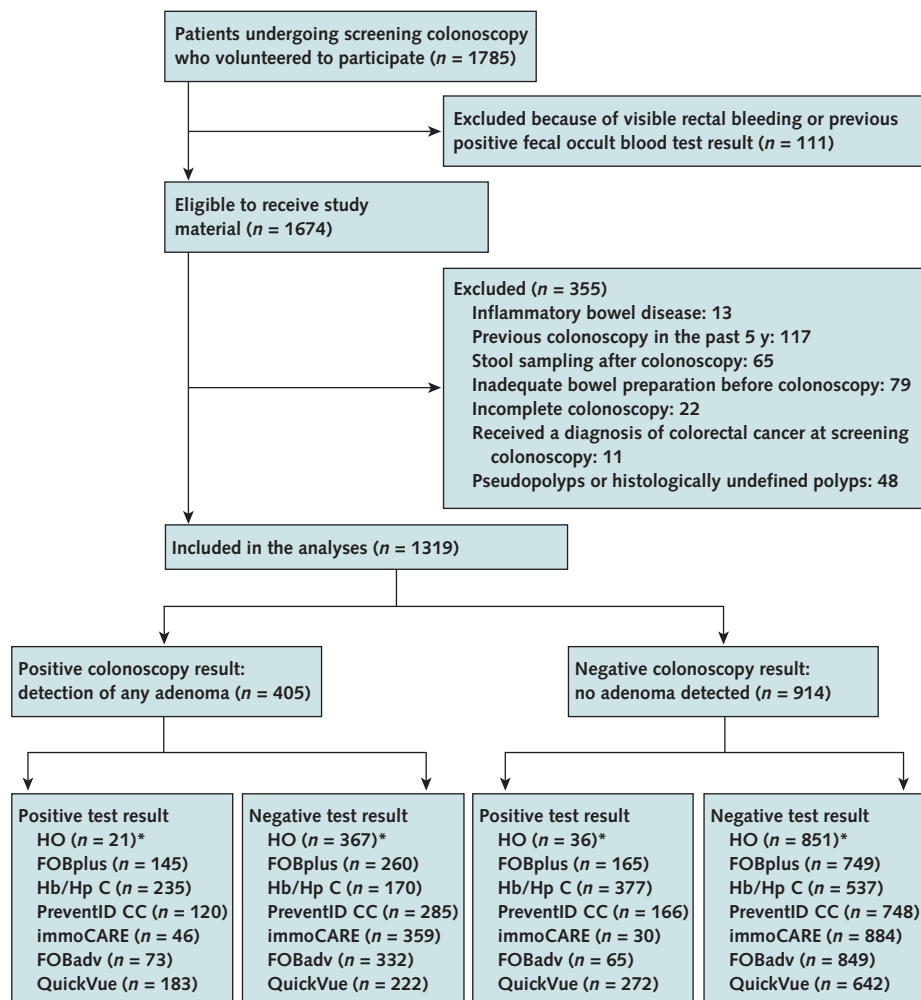
of 2007 and would not allow meaningfully precise performance estimates for this end point). Sensitivity with respect to CRC will be analyzed separately after continued recruitment of a much larger number of screening participants. We excluded 10 participants with nondefined polyps (no histologic reports were available) because we could not definitively determine the presence or absence of advanced adenomas in this group. Finally, we excluded participants with pseudopolyps ( $n = 38$ ) because these patients probably have had ulcerative colitis or undocumented inflammatory bowel disease.

**Stool Sample Collection**

Participants undergoing screening colonoscopy typically present at the gastroenterology practice for preliminary consultation about 1 week before colonoscopy. At that time, eligible patients received a study package that contained 1 test card for guaiac-based FOBT (HemOccult, Beckman Coulter, Krefeld, Germany), a small container (60 mL) for stool collection, a collection tissue for avoiding contact of the stool with toilet water, and detailed instructions for stool collection.

Stool samples were collected at home with no specific recommendations for diet or medicine restrictions. Patients received detailed instructions for sampling: Collect 1 bowel movement by using the collection tissue; apply stool with a spatula (provided in the study package) on 2 windows of 1 HemOccult test card and store the test card at room temperature; and fill at least half of the small container with stool by using plastic spoons (provided in the study pack-

Figure. Study flow diagram.



FOBadv = FOB advanced (ulti med, Ahrensburg, Germany); FOBplus = Bionexia FOBplus (DIMA, Göttingen, Germany); Hb/Hp C = Bionexia Hb/Hp Complex (DIMA); HO = HemOccult (Beckman Coulter, Krefeld, Germany); immoCare = immoCARE-C (CAREdiagnostica, Voerde, Germany); PreventID CC = PreventID CC (Preventis, Bensheim, Germany); QuickVue = QuickVue iFOB (Quidel, San Diego, California).

\* The exclusion of 44 patients overall was due to missing or noninterpretable test cards.

age), and store a plastic bag with the container in the freezer or, if not possible, in the refrigerator. Although the amount of stool provided varied widely, sufficient stool was available to adequately perform the different tests in all cases.

On the day of colonoscopy, patients provided the HemOccult test card and the stool-filled container at the gastroenterology practice. The latter was stored at  $-20^{\circ}\text{C}$ , then shipped on dry ice to a central laboratory and stored at  $-20^{\circ}\text{C}$  until analysis. We documented the dates of stool sampling, arrival at the central laboratory, and performance of the immunochemical FOBTs.

### Laboratory Analyses

Physician assistants who were blinded to the results of immunochemical testing analyzed HemOccult test cards at the gastroenterology practice on receipt according to the

manufacturer's instructions. They did analyses of HemOccult without rehydration, and test results were classified as positive, negative, or not interpretable (for example, owing to incorrect sampling).

We thawed the stool-filled containers at a median interval of 4 days on arrival at the central laboratory to do qualitative immunochemical FOBTs. Overall, we did 5 tests to determine fecal hemoglobin levels (Bionexia FOBplus, DIMA, Göttingen, Germany; PreventID CC, Preventis, Bensheim, Germany; immoCARE-C, CAREdiagnostica, Voerde, Germany; FOB advanced, ulti med, Ahrensburg, Germany; and QuickVue iFOB, Quidel, San Diego, California) and 1 test to determine both fecal hemoglobin and hemoglobin-haptoglobin levels (Bionexia Hb/Hp Complex, DIMA). All tests are based on immunochromatographic technology. The lower detection limits

indicated by the manufacturers were 10 ng/mL (PreventID CC), 25 ng/mL (Bionexia Hb/Hp Complex), 40 ng/mL (Bionexia FOBplus and FOB advanced), and 50 ng/mL (immoCARE-C and QuickVue iFOB).

We did all analyses according to the manufacturers' instructions and under standardized conditions. One trained investigator who was blinded to colonoscopy and HemOccult results classified all test results as positive or negative. Although classification was sometimes difficult for borderline results, we did not use an additional category for such results because the distinction between these and positive or negative results would be similarly difficult and partly subjective, given the continuum of underlying concentrations. Instead, we quantitatively evaluated uncertainty of test interpretation by assessing interrater reliability in a reliability study including 200 randomly selected samples. Two independent technicians interpreted all tests. Interobserver reliability was very good ( $\kappa$  coefficients, 0.94 [95% CI, 0.86 to 1.00] for Bionexia FOBplus, 0.86 [CI, 0.79 to 0.93] for the Hb test stripe and 0.72 [CI, 0.63 to 0.82] for the Hb/Hp test stripe of Bionexia Hb/Hp Complex, 0.92 [CI, 0.85 to 0.99] for PreventID CC, 0.97 [CI, 0.92 to 1.00] for immoCARE-C, 0.80 [CI, 0.71 to 0.89] for FOB advanced, and 0.91 [CI, 0.86 to 0.97] for QuickVue iFOB).

### Statistical Analyses

We calculated the specificity and sensitivity of the tests to detect an adenoma and, more specifically, advanced adenomas (adenomas  $\geq 1$  cm in diameter, adenomas with villous components, or adenomas with high-grade dysplasia) by using SAS software, version 9.1 (SAS Institute, Cary, North Carolina). On the basis of the exact binomial distribution, we calculated 95% CIs for sensitivities and specificities. We calculated predictive values and likelihood ratios (7) by using MedCalc for Windows, version 9.6.4.0 (MedCalc Software, Mariakerke, Belgium). We calculated CIs for likelihood ratios by using MedCalc, based on the log method described by Altman and colleagues (8). We used chi-square tests to compare proportions. In addition, we calculated sensitivities, stratified by location, number, and size of adenoma. Furthermore, we measured interobserver reliability by using  $\kappa$  statistics. Finally, we conducted sensitivity analyses to assess a potential role of sample handling and storage duration for test performance.

### Role of the Funding Source

The German Research Foundation (Deutsche Forschungsgemeinschaft) funded the study in the context of a PhD program (Graduiertenkolleg 793). The manufacturers provided stool test kits for free. The funding sources had no influence on study design, data collection, monitoring, analysis, and interpretation of results or the decision to submit the manuscript for publication.

## RESULTS

We included 1319 participants (mean age, 63 years; 50% men) in our analysis (Figure). Table 1 shows the distribution of sex, age, and findings on colonoscopy. An adenoma was detected in 405 (31%) participants, and an advanced adenoma was detected in 130 (10%) participants.

The Figure and Tables 2 and 3 show test results and performance indications of the different FOBTs. Total positivity rates ranged from 4.5% (HemOccult) to 46.4% (Bionexia Hb/Hp Complex). We found large differences in performance characteristics among the different immunochemical FOBTs. Sensitivity for the detection of any adenoma and advanced adenomas ranged from 11.4% to 58.0% and from 25.4% to 71.5%, respectively, and the difference between sensitivity and the false-positive rate was significant for all tests ( $P < 0.001$ ). When we combined patients with CRC ( $n = 11$ ) (who were excluded from the main analyses) with patients who had advanced adenomas, we found slightly higher estimates of sensitivity: 56.0% (CI, 47.4% to 64.4%) for Bionexia FOBplus, 73.8% (CI, 65.7% to 80.8%) for Bionexia Hb/Hp Complex, 53.2% (CI, 44.6% to 61.6%) for PreventID CC, 29.8% (CI, 22.4% to 38.1%) for immoCARE-C, 30.5% (CI, 23.0% to 38.8%) for FOB advanced, and 59.6% (CI, 51.0% to 67.8%) for QuickVue iFOB.

Specificity ranged from 58.8% to 96.7% and hardly changed when patients with hyperplastic polyps were ex-

**Table 1. Sample and Adenoma Characteristics**

Sample Characteristics	Mean Age, y	Participants, n (%)
Men	63.5	665 (50.4)
Women	62.4	654 (49.6)
Colonoscopic finding*		
Advanced adenoma†	65.7	130 (9.9)
Other adenoma	63.7	275 (20.8)
Hyperplastic polyp	63.4	125 (9.5)
No polyp	62.2	789 (59.8)
Adenoma Characteristics		
	Participants With Any Adenoma, n (%)‡	Participants With Advanced Adenoma, n (%)§
Location		
Proximal	156 (38.5)	42 (26.9)
Distal	174 (43.0)	55 (31.6)
Both	75 (18.5)	33 (44.0)
Number		
1	255 (63.0)	65 (25.5)
2	100 (24.7)	39 (39.0)
$\geq 3$	50 (12.3)	26 (52.0)
Diameter		
<1 cm	321 (79.3)	46 (14.3)
$\geq 1$ cm	84 (20.7)	84 (100.0)

\* Allocation to subgroups according to the most advanced finding at colonoscopy.  
 † Adenomas  $\geq 1$  cm in diameter, adenomas with villous components, or adenomas with high-grade dysplasia.

‡ Percentages are participants with any adenoma (derived from column values).  
 § Percentages are participants with any adenoma, by subgroup (derived from row values).

|| Proximal or distal to the splenic flexure.

**Table 2. Positivity Rates, Sensitivities, and Specificities of FOBTs**

Performance Characteristic	Immunochemical FOBT*						HemOccult Gualac-Based FOBT)*
	Bionexia FOBplus	Bionexia Hb/Hp Complex	PreventID CC	immoCARE-C	FOB advanced	QuickVue iFOB	
<b>Overall positivity rates</b>							
Patients, n/n†	310/1319	612/1319	286/1319	76/1319	138/1319	455/1319	57/1275
Percentage (95% CI)	23.5 (21.2–25.9)	46.4 (43.7–49.1)	21.7 (19.5–24.0)	5.8 (4.6–7.2)	10.5 (8.9–12.2)	34.5 (31.9–37.1)	4.5 (3.4–5.8)
<b>Sensitivity</b>							
Any adenoma							
Patients, n/n‡	145/405	235/405	120/405	46/405	73/405	183/405	21/388
Percentage (95% CI)	35.8 (31.1–40.7)	58.0 (53.1–62.9)	29.6 (25.2–34.3)	11.4 (8.4–14.9)	18.0 (14.4–22.1)	45.2 (40.3–50.2)	5.4 (3.4–8.2)
Advanced adenoma							
Patients, n/n‡	68/130	93/130	64/130	33/130	35/130	73/130	12/128
Percentage (95% CI)	52.3 (43.4–61.1)	71.5 (63.0–79.1)	49.2 (40.4–58.1)	25.4 (18.2–33.8)	26.9 (19.5–35.4)	56.2 (47.2–64.8)	9.4 (4.9–15.8)
Other adenoma							
Patients, n/n‡	77/275	142/275	56/275	13/275	38/275	110/275	9/260
Percentage (95% CI)	28.0 (22.8–33.7)	51.6 (45.6–57.7)	20.4 (15.8–25.6)	4.7 (2.5–8.0)	13.8 (10.0–18.5)	40.0 (34.2–46.1)	3.5 (1.6–6.5)
<b>Specificity</b>							
None or hyperplastic polyp							
Patients, n/n§	749/914	537/914	748/914	884/914	849/914	642/914	851/887
Percentage (95% CI)	81.9 (79.3–84.4)	58.8 (55.5–62.0)	81.8 (79.2–84.3)	96.7 (95.4–97.8)	92.9 (91.0–94.5)	70.2 (67.2–73.2)	95.9 (94.4–97.1)

FOBT = fecal occult blood test.

\* For manufacturer information, see the Figure.

† Patients with a positive test result/all patients.

‡ Patients with a positive test result/all patients with this finding.

§ Patients with a negative test result/all patients with negative findings on colonoscopy.

cluded from the control group. We found specificities greater than 90% for only 2 tests (immoCARE-C and FOB advanced), which allowed detection of 25.4% and 26.9% of advanced adenomas, respectively. Although the specificity of immoCARE-C was higher than that of FOB advanced (96.7% vs. 92.9%), the latter showed a higher sensitivity for other adenomas (13.8% vs. 4.7%) and for any adenoma (18.0% vs. 11.4%). Bionexia FOBplus and PreventID CC had a specificity greater than 80% and a sensitivity for advanced adenomas of about 50%, whereas QuickVue iFOB and Bionexia Hb/Hp Complex had the lowest specificities (about ≤ 70%) and the highest sensitivities. The sensitivity of the guaiac-based HemOccult test (1-day sampling) for the detection of advanced adenomas was about 9%, and specificity was 96%.

Positive predictive values for the various immunochemical FOBTs with respect to any adenoma ranged from 40.2% (QuickVue iFOB) to 60.5% (immoCARE-C), whereas the range of negative predictive values was narrow, from 71.1% (immoCARE-C) to 76.0% (Bionexia Hb/Hp Complex) (Table 3). For immoCARE-C, we found the highest positive predictive value and the highest likelihood ratios for the detection of any adenoma.

Table 4 shows sensitivities, stratified by location, number, and size of adenoma. For all immunochemical FOBTs, sensitivity increased with greater number and size of adenomas, which is strongly related to the proportions of advanced adenomas in the different subgroups (Table 1). Furthermore, most tests showed higher sensitiv-

ity for distal adenomas than for proximal adenomas (except for QuickVue iFOB and HemOccult), even though the proportion of advanced adenomas was almost the same in both groups (Table 1). The difference by location was significant for PreventID CC ( $P = 0.022$ ), immoCARE-C ( $P = 0.017$ ), and FOB advanced ( $P = 0.041$ ).

To explore possible effects due to variation in the duration of interim sample storage, we assessed sensitivity and specificity for detection of advanced adenomas, stratified by tertiles of storage duration. Stool samples arrived at the central laboratory after a median of 7 days, and samples were stored at the central laboratory for a median of 4 days. Overall, the median interval between stool sampling and performance of immunochemical FOBTs was 13 days. Apart from random variation, which resulted from the smaller sample sizes in the different subgroups, no general trend in either direction could be found for sensitivity or specificity (Appendix Tables 1 to 3, available at [www.annals.org](http://www.annals.org)).

We assessed the effect of following storage instructions by excluding nonfrozen samples or samples without explicit storage documentation. Whether stool samples were frozen at home as recommended until they were brought to the gastroenterology practice was explicitly documented for 961 (73.0%) of 1319 samples. Forty-nine (4%) participants reported that freezing was not possible. Sensitivity analyses did not indicate any relevant differences from the results obtained in the entire study sample (Appendix Table 4, available at [www.annals.org](http://www.annals.org)).

## DISCUSSION

Stool tests are an important component of the options recommended for CRC screening (9). They are particularly relevant for patients who would not be willing to have screening colonoscopy or in a setting in which colonoscopy is not offered as a primary screening tool (for example, because of limited resources). In comparing 6 different qualitative immunochemical FOBTs in parallel among participants undergoing screening colonoscopy, we found marked differences in test performance characteristics for the detection of colorectal adenomas. We found promising results for 2 tests (immoCARE-C and FOB advanced) that showed 25% and 27% sensitivity, respectively, for advanced adenomas and greater than 90% specificity (immoCARE-C, 96.7%; FOB advanced, 92.9%). FOB advanced was more sensitive for other adenomas, and immoCARE-C had the highest specificity. Further analyses by location, number, and size of adenoma revealed higher sensitivities for distal, large, and several adenomas.

We found similarly designed studies, in which all participants had endoscopy, that were published in English until August 2008 by searching MEDLINE. These studies also reported similar or inferior sensitivity at similar specificity. The most important study for comparison included 21 805 asymptomatic participants who had colonoscopy (10). In this study, a quantitative immunochemical FOBT based on the magnetic agglutination technique (Magstream 1000/Hem SP, Fujirebio Diagnostics, Tokyo, Japan) was evaluated and showed a sensitivity of 22.3% for advanced neoplasia (excluding invasive CRC) and a specificity of 95.5%.

A qualitative immunochemical FOBT based on immunochromatographic technology (FlexSure OBT, Beckman Coulter, Palo Alto, California) has been evaluated in comparison with endoscopy in 5841 participants at average risk for CRC (11). However, the study design allowed evaluation of detecting distal lesions only because sigmoidoscopy and not colonoscopy was typically done in test-negative patients within 2 years after stool testing. Sensitivity of this test for distal large adenomas ( $\geq 1$  cm in diameter) was 29.5%, whereas specificity was 97.3%.

Although various other endoscopy-based studies have been done to evaluate immunochemical FOBTs, the samples comprised mostly symptomatic participants or participants with previous polypectomy (12–19). Performance characteristics in these studies also varied greatly: Sensitivities for advanced adenomas ranged from 30% to 50%, and specificities ranged from 86% to 98%. However, these results may not apply to asymptomatic patients in the screening setting. Furthermore, only a few studies evaluated different immunochemical FOBTs in parallel, and they typically had small samples (16, 19).

Although differences in samples may partly explain the large variation of performance characteristics of tests across studies, the reason for the large variation across tests in our study are less clear. In particular, the different detection limits indicated by the manufacturers could hardly and not consistently explain this variation. Further potential explanations, such as the effect of the antibodies or the solution buffer, need to be explored. The strengths of our study include that all participants had colonoscopy, regardless of FOBT results, and the large sample. Because we included only participants undergoing screening colonoscopy (we excluded patients who reported visible or occult bleeding or inflammatory bowel disease and those who reported having had colonoscopy in the past 5 years), we assessed test performance characteristics in the target population of screening, that is, for the distribution of age and of risk profiles. The distribution of findings at colonoscopy (percentage of adenomas) was in accordance with other studies, including those conducted among attendees of screening colonoscopy (16, 20). Furthermore, because our study evaluated different qualitative immunochemical FOBTs in parallel, it is a timely contribution to optimize tools for CRC screening, given the advantages of these tests for practicality compared with quantitative immunochemical FOBTs.

A limitation of our setting was that stool from only 1 day was collected and used for analyses, which could have led to underestimation of sensitivities and slight overestimation of specificities, as Nakama and coworkers found (21, 22). According to the manufacturers' instructions for the tests used in our study, 1-day sampling was recom-

Table 3. Predictive Values and Likelihood Ratios of Different FOBTs

Performance Characteristic	Immunochemical FOBT*						HemOccult (Guaiac-Based FOBT)*
	Bionexia FOBplus	Bionexia Hb/Hp Complex	PreventID CC	immoCARE-C	FOB advanced	QuickVue iFOB	
<b>Predictive value for any adenoma (95% CI), %</b>							
Positive	46.8 (41.1–52.5)	38.4 (34.5–42.4)	42.0 (36.2–47.9)	60.5 (48.7–71.6)	52.9 (44.2–61.5)	40.2 (35.7–44.9)	32.1 (19.9–46.3)
Negative	74.2 (71.4–76.9)	76.0 (72.6–79.0)	72.4 (69.6–75.1)	71.1 (68.5–73.6)	71.9 (69.2–74.4)	74.3 (71.2–77.2)	69.9 (67.2–72.4)
<b>Likelihood ratio for any adenoma (95% CI), %</b>							
Positive	1.98 (1.64–2.40)	1.41 (1.26–1.58)	1.63 (1.33–2.00)	3.46 (2.22–5.40)	2.53 (1.85–3.47)	1.52 (1.31–1.76)	1.09 (0.62–1.92)
Negative	0.78 (0.72–0.85)	0.71 (0.63–0.81)	0.86 (0.80–0.92)	0.92 (0.88–0.95)	0.88 (0.84–0.93)	0.78 (0.71–0.86)	1.00 (0.97–1.02)

FOBT = fecal occult blood test.

\* For manufacturer information, see the Figure.

**Table 4. Sensitivities of Different FOBTs for the Detection of Adenomas, Stratified by Location, Number, and Size of Adenoma**

Sensitivity (95% CI)	Immunochemical FOBT*						HemoOccult (Guaiac-Based FOBT)*
	Bionexia FOBplus	Bionexia Hb/Hp Complex	PreventID CC	immoCARE-C	FOB advanced	QuickVue iFOB	
<b>Location of adenoma, %†</b>							
Proximal	28.9 (21.9–36.6)	50.6 (42.5–58.7)	20.5 (14.5–27.7)	5.1 (2.2–9.9)	10.9 (6.5–16.9)	43.0 (35.1–51.1)	6.1 (2.8–11.3)
Distal	35.1 (28.0–42.6)	59.8 (52.2–67.1)	31.6 (24.8–39.1)	12.6 (8.1–18.5)	19.0 (13.4–25.6)	42.5 (35.1–50.2)	4.2 (1.7–8.4)
<b>Number of adenomas, %</b>							
1	27.8 (22.4–33.8)	53.3 (47.0–59.6)	23.5 (18.5–29.2)	7.8 (4.9–11.9)	13.7 (9.8–18.6)	38.4 (32.4–44.7)	5.8 (3.2–9.5)
2	46.0 (36.0–56.3)	65.0 (54.8–74.3)	38.0 (28.5–48.3)	14.0 (7.9–22.4)	25.0 (16.9–34.7)	52.0 (41.8–62.1)	3.1 (0.6–8.7)
≥3	56.0 (41.3–70.0)	68.0 (53.3–80.5)	44.0 (30.0–58.8)	24.0 (13.1–38.2)	26.0 (14.6–40.3)	66.0 (51.2–78.8)	8.3 (2.3–20.0)
<b>Diameter of largest adenoma, %</b>							
<1 cm	29.6 (24.7–34.9)	52.0 (46.4–57.6)	22.7 (18.3–27.7)	5.6 (3.4–8.7)	14.0 (10.4–18.3)	38.6 (33.3–44.2)	3.3 (1.6–5.9)
≥1 cm	59.5 (48.3–70.1)	81.0 (70.9–88.7)	56.0 (44.7–66.8)	33.3 (23.4–44.5)	33.3 (23.4–44.5)	70.2 (59.3–79.7)	13.4 (6.9–22.7)

FOBT = fecal occult blood test.  
 \* For manufacturer information, see the Figure.  
 † Category “both” not considered.

mended, except for the guaiac-based HemOccult (which required 3-day sampling and diet and medication restriction). However, differences in sensitivities between guaiac-based FOBT and immunochemical FOBTs were very large and cannot be explained by this procedural limitation only; furthermore, multiple sampling would influence diagnostic performance of immunochemical FOBTs as well. Stool sampling in our study somewhat differed from real-life conditions because stool was not directly dissolved in a buffer-filled vial but was instead collected in a small container and frozen before testing. The instruction manuals typically suggest directly using fresh stool, but this might be recommended to meet practical applications for the patient. Whether stool samples were frozen or not is expected to affect performance of guaiac-based FOBTs which are based on the pseudoperoxidase activity of hemoglobin and require an intact molecule. Thus, stool samples used for guaiac-based tests should not be frozen (the latter was ensured in our study for the HemOccult). In contrast, for immunochemical FOBTs, only parts of the molecule are typically important for the detection of hemoglobin levels, and the potential degradation due to freezing is therefore not expected to affect test performance. The results of our sensitivity analyses are consistent with these expectations. Furthermore, because sample handling in our study was the same for all immunochemical FOBTs, the comparison among tests should not be limited.

Selection bias is a concern in any screening study. We tried to minimize selection bias by using inclusion and exclusion criteria that aimed for maximum possible representativeness of study participants for the target population of stool-based primary CRC screening. In particular, recruitment was done in 20 centers in the routine screening setting. However, participants undergoing screening colonoscopy may be more health conscious than the gen-

eral population, which must be kept in mind for the generalizability of results.

Our study might be limited by the accuracy of colonoscopy for the detection of precancerous lesions in routine practice (23). In Germany, high levels of qualification and experience are a prerequisite for conducting screening colonoscopies. Only experienced endoscopists (internists or gastroenterologists or surgeons with pertinent certified specializations who have conducted at least 200 colonoscopies and at least 50 polypectomies under supervision in the preceding 2 calendar years) are approved. This setting should ensure reasonable, albeit not perfect, accuracy of colonoscopy findings.

In conclusion, our results demonstrate that qualitative immunochemical FOBTs could be an option for future CRC screening, combining the advantages of immunochemical FOBT (improved detection of precancerous lesions) with the same or greater simplicity and practicality for mass screening as offered by the widely used guaiac-based FOBT. Careful evaluation of each test variant, is needed, given the large differences in diagnostic performance among tests. Only 2 of the tests showed specificity typically required for routine testing of average-risk populations to minimize follow-up colonoscopies.

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**Appendix Table 1. Sensitivity and Specificity of Immunochemical Fecal Occult Blood Tests, Stratified by Time From Collection of the Stool Sample to Its Arrival at the Central Laboratory\***

Performance Characteristic	Bionexia FOBplus	Bionexia Hb/Hp Complex	PreventID CC	immoCARE-C	FOB advanced	QuickVue iFOB
<b>≤5 days from collection to arrival</b>						
Sensitivity (95% CI), %						
Advanced adenoma	60.0 (40.6–77.3)	93.3 (77.9–99.0)‡	53.3 (34.3–71.6)	20.0 (7.7–38.6)	26.7 (12.3–45.9)	60.0 (40.6–77.3)‡
Other adenoma	22.2 (13.3–33.6)†	51.4 (39.3–63.4)	25.0 (15.5–36.6)‡	5.6 (1.5–13.6)	11.1 (4.9–20.7)†	43.1 (31.4–55.3)‡
Specificity (95% CI), %						
None or hyperplastic polyp	80.5 (75.2–85.0)†	55.3 (49.1–61.3)†	82.7 (77.6–87.1)	95.2 (92.0–97.5)†	91.4 (87.3–94.4)†	68.8 (62.9–74.3)†
<b>6–9 days from collection to arrival</b>						
Sensitivity (95% CI), %						
Advanced adenoma	37.0 (23.2–52.5)†	58.7 (43.2–73.0)†	32.6 (19.5–48.0)†	13.0 (5.0–26.3)†	21.7 (11.0–36.4)†	52.2 (37.0–67.1)†
Other adenoma	36.6 (25.5–48.9)‡	60.6 (48.3–72.0)‡	21.1 (12.3–32.4)	7.0 (2.4–15.7)‡	16.9 (9.1–27.7)‡	42.3 (30.6–54.6)
Specificity (95% CI), %						
None or hyperplastic polyp	84.9 (79.9–89.0)‡	60.9 (54.6–66.9)‡	83.7 (78.6–88.0)‡	97.3 (94.5–98.9)‡	94.6 (91.1–97.0)‡	70.9 (65.0–76.4)‡
<b>&gt;9 days from collection to arrival</b>						
Sensitivity (95% CI), %						
Advanced adenoma	62.8 (46.7–77.0)‡	67.4 (51.5–80.9)	58.1 (42.1–73.0)‡	34.9 (21.0–51.0)‡	27.9 (15.3–43.7)‡	58.1 (42.1–73.0)
Other adenoma	29.5 (20.6–39.7)	46.3 (36.0–56.8)†	19.0 (11.6–28.3)†	3.2 (0.7–9.0)†	14.8 (8.3–23.5)	37.9 (28.1–48.4)†
Specificity (95% CI), %						
None or hyperplastic polyp	80.6 (75.7–84.9)	59.9 (54.1–65.5)	80.3 (75.3–84.6)†	97.0 (94.4–98.6)	92.0 (88.3–94.8)	70.2 (64.7–75.4)

\* For manufacturer information, see the Figure.

† Lowest values for sensitivity and specificity.

‡ Highest values for sensitivity and specificity.

**Appendix Table 2. Sensitivity and Specificity of Immunochemical Fecal Occult Blood Tests, Stratified by Time From Arrival of the Stool Sample at the Central Laboratory to Its Analysis\***

Performance Characteristic	Bionexia FOBplus	Bionexia Hb/Hp Complex	PreventID CC	immoCARE-C	FOB advanced	QuickVue iFOB
<b>&lt;2 days from arrival to analysis</b>						
Sensitivity (95% CI), %						
Advanced adenoma	51.7 (38.2–65.1)	80.7 (68.1–90.0)‡	43.1 (30.2–56.8)†	27.6 (16.7–40.0)‡	31.0 (19.6–44.6)‡	69.1 (55.2–80.9)‡
Other adenoma	24.3 (16.4–33.7)†	45.9 (35.8–56.3)†	20.4 (13.1–29.5)	3.9 (1.1–9.7)†	10.7 (5.5–18.3)†	36.8 (26.7–47.8)†
Specificity (95% CI), %						
None or hyperplastic polyp	83.6 (79.3–87.3)‡	59.2 (53.8–64.4)	81.6 (77.2–85.5)	96.9 (94.5–98.4)‡	95.2 (92.4–97.2)‡	71.5 (66.1–76.4)‡
<b>2–7 days from arrival to analysis</b>						
Sensitivity (95% CI), %						
Advanced adenoma	44.8 (26.5–64.3)†	66.7 (46.0–83.5)	44.8 (26.5–64.3)	20.7 (8.1–39.7)†	20.7 (8.1–39.7)†	59.3 (38.8–77.6)
Other adenoma	30.6 (20.2–42.5)‡	55.6 (43.4–67.3)‡	23.6 (14.4–35.1)‡	4.2 (0.9–11.7)	11.1 (5.0–20.7)	41.7 (30.2–53.9)‡
Specificity (95% CI), %						
None or hyperplastic polyp	80.2 (74.6–85.0)†	59.8 (53.3–66.0)‡	80.2 (74.6–85.0)†	96.4 (93.2–98.3)†	92.3 (88.3–95.3)	70.3 (64.2–76.0)
<b>&gt;7 days from arrival to analysis</b>						
Sensitivity (95% CI), %						
Advanced adenoma	58.1 (42.1–73.0)‡	63.0 (47.6–76.8)†	60.5 (44.4–75.0)‡	25.6 (13.5–41.2)	25.6 (13.5–41.2)	39.6 (25.8–54.7)†
Other adenoma	30.0 (21.2–40.0)	54.3 (44.3–64.0)	18.0 (11.0–27.0)†	6.0 (2.3–12.6)‡	19.0 (11.9–28.1)‡	41.4 (32.3–50.9)
Specificity (95% CI), %						
None or hyperplastic polyp	81.1 (76.3–85.3)	58.0 (52.3–63.5)†	84.0 (79.5–88.0)‡	96.7 (94.1–98.4)	90.6 (86.7–93.6)†	69.1 (64.0–74.0)†

\* For manufacturer information, see the Figure.

† Lowest values for sensitivity and specificity.

‡ Highest values for sensitivity and specificity.

**Appendix Table 3. Sensitivity and Specificity of Immunochemical Fecal Occult Blood Tests, Stratified by Time From Collection of the Stool Sample to Its Analysis\***

Performance Characteristic	Bionexia FOBplus	Bionexia Hb/Hp Complex	PreventID CC	immoCARE-C	FOB advanced	QuickVue iFOB
<b>≤9 days from collection to analysis</b>						
Sensitivity (95% CI), %						
Advanced adenoma	41.5 (26.3–57.9)†	80.0 (64.4–90.9)‡	34.2 (20.1–50.6)†	17.1 (7.2–32.1)†	24.4 (12.4–40.3)	69.2 (52.4–83.0)‡
Other adenoma	21.2 (12.1–33.0)†	40.3 (28.1–53.6)†	24.2 (14.5–36.4)‡	3.0 (0.5–10.5)†	3.0 (0.5–10.5)†	28.1 (17.0–41.5)†
Specificity (95% CI), %						
None or hyperplastic polyp	82.4 (77.4–86.7)	57.7 (51.6–63.7)†	81.0 (75.8–85.4)†	95.6 (92.5–97.7)†	94.1 (90.7–96.6)	69.7 (63.6–75.3)
<b>10–20 days from collection to analysis</b>						
Sensitivity (95% CI), %						
Advanced adenoma	64.1 (47.2–78.8)‡	73.0 (55.9–86.2)	51.3 (34.8–67.6)	28.2 (15.0–44.9)‡	30.8 (17.0–47.6)‡	63.9 (46.2–79.2)
Other adenoma	36.7 (26.8–47.5)‡	60.0 (49.1–70.2)‡	22.2 (14.1–32.2)	6.7 (2.5–14.0)‡	17.8 (10.5–27.3)	50.0 (39.0–61.0)‡
Specificity (95% CI), %						
None or hyperplastic polyp	79.8 (74.6–84.4)†	59.0 (52.9–65.0)	81.6 (76.5–86.0)	97.5 (94.9–99.0)‡	94.6 (91.2–97.0)‡	71.7 (65.7–77.1)
<b>&gt;20 days from collection to analysis</b>						
Sensitivity (95% CI), %						
Advanced adenoma	52.6 (35.8–69.0)	61.0 (44.5–75.8)†	57.9 (40.8–73.7)‡	23.7 (11.5–40.3)	21.1 (9.6–37.3)†	39.5 (25.0–55.6)†
Other adenoma	26.6 (17.3–37.7)	51.8 (40.6–62.9)	17.7 (10.1–28.0)†	5.1 (1.4–12.5)	20.2 (12.1–30.8)‡	39.1 (29.2–50.0)
Specificity (95% CI), %						
None or hyperplastic polyp	83.6 (78.6–87.8)‡	59.6 (53.6–65.4)‡	84.0 (79.0–88.1)‡	96.6 (93.7–98.5)	89.2 (84.8–92.6)†	68.8 (63.4–73.9)†

\* For manufacturer information, see the Figure.

† Lowest values for sensitivity and specificity.

‡ Highest values for sensitivity and specificity.

**Appendix Table 4. Sensitivity Analyses to Assess the Effect of Excluding Patients Who Provided Nonfrozen Stool Samples ( $n = 51$ ) and Patients Who Did Not Provide Explicit Documentation of Storage Conditions ( $n = 358$ ) on Test Performance Characteristics\***

Performance Characteristic	Bionexia FOBplus	Bionexia Hb/Hp Complex	PreventID CC	immoCARE-C	FOB advanced	QuickVue iFOB
<b>Inclusion of all stool samples</b>						
Sensitivity						
Advanced adenoma						
Patients, $n/n^\dagger$	68/130	93/130	64/130	33/130	35/130	73/130
Percentage (95% CI)	52.3 (43.4–61.1)	71.5 (63.0–79.1)	49.2 (40.4–58.1)	25.4 (18.2–33.8)	26.9 (19.5–35.4)	56.2 (47.2–64.8)
Other adenoma						
Patients, $n/n^\dagger$	77/275	142/275	56/275	13/275	38/275	110/275
Percentage (95% CI)	28.0 (22.8–33.7)	51.6 (45.6–57.7)	20.4 (15.8–25.6)	4.7 (2.5–8.0)	13.8 (10.0–18.5)	40.0 (34.2–46.1)
Specificity						
None or hyperplastic polyp						
Patients, $n/n^\ddagger$	749/914	537/914	748/914	884/914	849/914	642/914
Percentage (95% CI)	81.9 (79.3–84.4)	58.8 (55.5–62.0)	81.8 (79.2–84.3)	96.7 (95.4–97.8)	92.9 (91.0–94.5)	70.2 (67.2–73.2)
<b>After exclusion of nonfrozen stool samples or stool samples without explicit documentation of storage conditions</b>						
Sensitivity						
Advanced adenoma						
Patients, $n/n^\dagger$	47/89	64/89	44/89	22/89	25/89	52/89
Percentage (95% CI)	52.8 (41.9–63.5)	71.9 (61.4–80.9)	49.4 (38.7–60.3)	24.7 (16.2–35.0)	28.1 (19.1–38.6)	58.4 (47.5–68.8)
Other adenoma						
Patients, $n/n^\dagger$	63/199	108/199	46/199	10/199	30/199	85/199
Percentage (95% CI)	31.7 (25.3–38.6)	54.3 (47.2–61.3)	23.1 (17.5–29.6)	5.0 (2.4–9.1)	15.1 (10.4–20.8)	42.7 (35.7–49.9)
Specificity						
None or hyperplastic polyp						
Patients, $n/n^\ddagger$	507/622	355/622	505/622	597/622	574/622	429/622
Percentage (95% CI)	81.5 (78.3–84.5)	57.1 (53.1–61.0)	81.2 (77.9–84.2)	96.0 (94.2–97.4)	92.3 (89.9–94.3)	69.0 (65.2–72.6)

\* For manufacturer information, see the **Figure**.

† Patients with a positive test result/all patients with this finding.

‡ Patients with a negative test result/all patients with negative findings on colonoscopy.