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Both Sample Number and Test Positivity Threshold Determine Colonoscopy Efficiency in Detection of Colorectal Cancer With Quantitative Fecal Immunochemical Tests

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The fecal hemoglobin concentration varies between colorectal pathologies and between samples because bleeding is not consistent from day to day.[1] Thus, when screening for colorectal cancer (CRC) using a quantitative fecal immunochemical test (FIT), the fecal hemoglobin concentration threshold (cutoff) chosen to trigger colonoscopy,[2] together with the number of stools sampled, are crucial variables requiring careful selection, because of the implications for sensitivity, specificity, colonoscopic workload, and cost effectiveness.[3]

In a CRC surveillance population, all of whom did a 2-sample FIT (2-FIT) preceding a scheduled colonoscopy, we explored the interplay between the variables of sample number and cutoff and how they affected the programmatically important outcomes of colonoscopic workload, lesion detection (sensitivity for CRC and advanced adenoma [AA]), and colonoscopic effort needed to detect 1 lesion (a key determinant of cost effectiveness).[4]

Methods

From a large population (N = 19,229) at increased risk for CRC and under surveillance with intermittently scheduled colonoscopy[5] plus 2-FIT in the intervening years, we retrospectively identified all patients who had correctly completed a 2-FIT (OC-Sensor, Eiken Chemical Company, Japan) within 12 months before a high-quality colonoscopy. FIT test positivity rate (colonoscopy workload), sensitivity for advanced neoplasia (CRC plus AA), and number in the population needing to undergo colonoscopy to detect 1 case with advanced neoplasia (effort) was modeled across a wide range of cutoffs (10–150 μg hemoglobin [Hb]/g feces) in the settings of 1- and 2-sample testing. Details are provided in Supplementary Materials.

Results

Participants

In addition to undergoing colonoscopy, 12,710 patients completed a 2-FIT (56.9% male; median age; 66.5 y; interquartile range [IQR], 60.9–70.6 y) on 32,413 occasions. Overall, 7.04% had positive results considering a 2-sample test (either positive) and a cutoff of 20 μg Hb/g. The positivity rate for the first sample collected was 4.42% at the same cutoff.

Of these, 3349 (49.2% male; median age, 64.0 y; IQR, 57.3–69.6 y) completed a 2-FIT in the year prior (median, 152 d; IQR, 69–291 d) to colonoscopy on 4244 occasions. After exclusions, 4037 episodes were eligible for outcome modeling. Advanced neoplasia was diagnosed in 15.5% (n = 626) of the episodes, which included 0.5% CRC (n = 21) and 15.0% AA (n = 605), whereas nonadvanced adenomas of any type were detected in 29.7% (n = 1199). Rates of advanced neoplasia (12.3%) and nonadvanced adenoma (34.1%) were similar in those who completed FIT outside of the 1-year window (n = 9361).

Effect of Varying Sample Number and Cutoff on Sensitivity and Workload

Figure 1 shows how sensitivity for advanced neoplasia and the population colonoscopy workload (the FIT positivity rate observed in all those completing 2-FIT) was affected by sample number and cutoff. Sensitivity varied from 5% to 62% according to cutoff and sample number (Figure 1). Adenoma sensitivity was most compromised by changing the cutoff. For cutoffs of 10–80 μg Hb/g, 2-FIT sensitivity for CRC dropped from 81% to 61.9%, compared to a steeper drop for AA of 59.0% to 16.2%; 1-sample FIT (1-FIT) rates fell in parallel. The rate of increase in sensitivity slowed for both 1- and 2-FIT with cutoffs of 20 μg Hb/g and lower. In contrast, the colonoscopy workload continued to increase even more rapidly, identifying a loss of efficiency in lesion detection at cutoffs of 20 μg Hb/g and lower.

Effect of Varying Sample Number and Cutoff on Colonoscopy Effort

Supplementary Table 1 shows that the greatest colonoscopic effort (number needed to undergo colonoscopy to find 1 case with advanced neoplasia) was observed at the

Abbreviations used in this paper: **1-FIT, 1-sample fecal immunochemical test for hemoglobin; 2-FIT, 2-sample fecal immunochemical test for hemoglobin; AA, advanced adenoma; CRC, colorectal cancer; FIT, fecal immunochemical test for hemoglobin; Hb, hemoglobin; IQR, interquartile range.**

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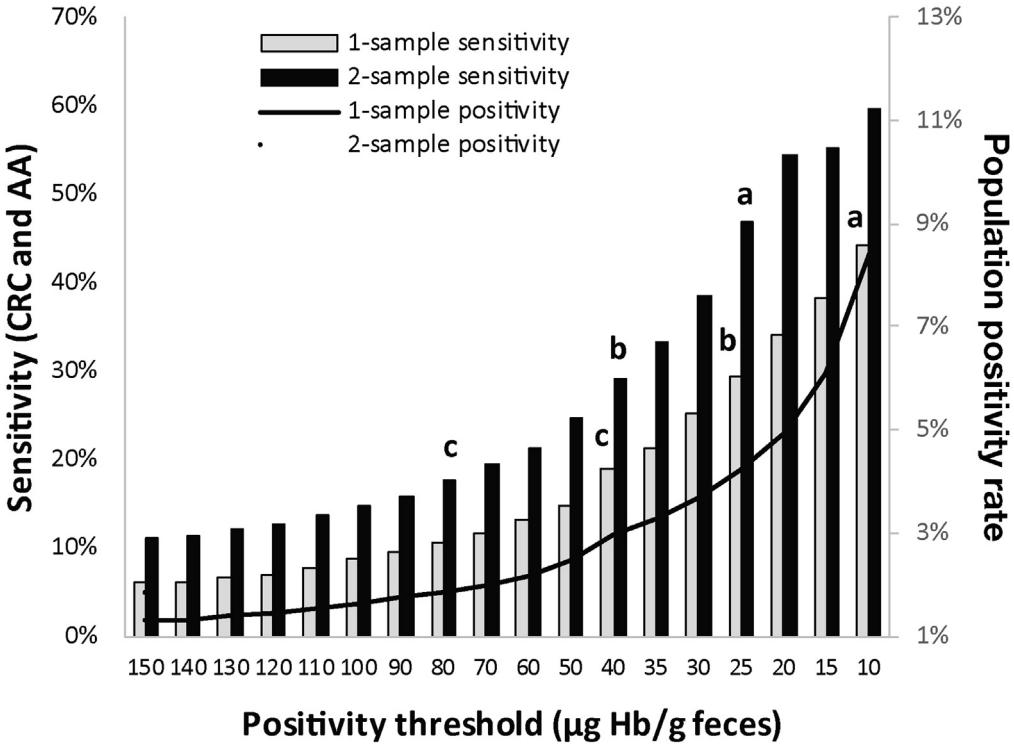

Figure 1. Sensitivity for advanced neoplasia (CRC and AA) and total population positivity rate (colonoscopy workload) across a wide range of fecal immunochemical test cutoffs (positivity thresholds) and according to 1- and 2-sample approaches. See the text and Supplementary Table 1 for modeling a comparison of the cutoff/sample number pairs with similar sensitivities identified by a letter pairs (a, b, or c).

lowest cutoff value (10 μg Hb/g) for either sample number (10.49 and 9.29 for 2-FIT and 1-FIT, respectively), whereas effort (range, 6.51–7.33) for the other cutoff/sample number combinations was lower with nonoverlapping confidence intervals.

Therefore, we compared colonoscopic effort and workloads for sample number/cutoff pairs returning a similar sensitivity. Three sets of conditions (pairs marked a, b, and c in Figure 1) are selected to show differences between the 1- and 2-sample approaches. For instance, when seeking a high sensitivity for advanced neoplasia, use of 1-FIT at a cutoff 10 μg Hb/g (column pair a in Figure 1) returned a sensitivity of 44.1% and a population test positivity rate (colonoscopy workload) of 7.9%. However, 2-FIT, at the higher cutoff of 25 μg Hb/g, achieved a similar sensitivity of 46.6% but at a lower colonoscopy workload rate of just 5.9% (Supplementary Table 1). The number needed to undergo colonoscopy was also significantly lower for the 2-sample approach (6.59 vs 9.29) (Supplementary Table 1 and Supplementary Figure 1). For sample number/cutoff pairs b and c, which returned significantly lower sensitivities for advanced neoplasia (Figure 1 and Supplementary Table 1), the workload and efficiency gains were not apparent for the 2-sample approach.

Discussion

Sensitivity for advanced neoplasia and population colonoscopic workload are directly related to both test cutoff and sample number, but our findings show that the relationship of these variables with colonoscopic effort is more complex based on modeling in this surveillance population. Basing choice solely on cut-off for a 1-sample FIT (1-FIT) is often done to control colonoscopy workload,[3,6] but our findings show that with 2-FIT set at a similar sensitivity for advanced neoplasia, the associated colonoscopic workload is no higher, whereas colonoscopic effort per lesion detected (and its cost-benefit implications) is less. Specifically, the effort required using 2-FIT at a cutoff 25 μg Hb/g was significantly less than using 1-FIT at 10 μg Hb/g, and each condition returned a similar sensitivity.

This principle applies particularly when aiming to detect as many AAs as possible in addition to CRC because FIT sensitivity for AA dropped rapidly at cutoffs higher than 25μg Hb/g. Although most countries are undertaking 1-FIT screening,[6] we lack conclusive evidence to support the notion that participation in screening is improved when requiring just 1 sample.[7] Although these data are derived from an elevated risk population, the study's strengths are that all patients did 2-FIT and all had complete diagnostic verification. Furthermore, the overall test result positivity rate for 1- and 2-FIT was similar to that reported for a Scandinavian screening population.[8] Careful choice of both the FIT cutoff value for positivity and of the number of stools to be sampled is necessary when considering workload capacity and the effort required to detect advanced colorectal neoplasia.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2020.05.008.

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Erin L Symonds, PhD (Conceptualization: Equal; Data curation: Lead; Formal analysis: Supporting; Project administration: Lead; Validation: Lead; Writing – review & editing: Equal).

Conflicts of interest
This author discloses the following: Graeme P. Young has received institutional research support from Eiken Chemical Company, Tokyo, Japan. The remaining authors disclose no conflicts.

Supplementary Materials and Methods

Population

Participants were enrolled in a colonoscopy and interval FIT surveillance program personalized for risk for CRC—the Southern Cooperative Program for Prevention of Colorectal Cancer (SCOOP) program[1–3]—during the period from July 2008 to April 2019. Enrollment was determined by their physician according to whether their risk (based on personal or family history of neoplasia) was sufficient to justify intermittent colonoscopy (usually every 3 or 5 years) according to Australian guidelines in operation at the time.[4] In addition to everyone receiving regular colonoscopy, individuals were provided with the opportunity to complete a 2-FIT between scheduled colonoscopies. The SCOOP program and how it is managed using a centralized database have been previously described in detail.[2,3] The database includes demographic details, risk status, details of colorectal pathology, and quantitative FIT results. The indication for being in the program was personal history of colorectal neoplasia for 8563 (68.1%) participants and family history of CRC for all others.

Individuals eligible for inclusion in the modeling were those who had undergone a colonoscopy (regardless of the FIT result) and who had returned a 2-sample FIT test kit in the preceding 365 days. Individuals were excluded if there had been an incomplete colonoscopy, one with a poor preparation, or any uncertainty with regard to the nature of the neoplasm found; if the patient was diagnosed with inflammatory bowel disease or a genetic syndrome (FAP or Lynch syndrome); if the FIT was done incompletely or incorrectly; or if there had been failure of sample development.

Approval for the study was obtained from the Southern Adelaide Clinical Human Research Ethics Committee (ethics no. 422.13). Its deliberations are consistent with the Helsinki Declaration.[5]

Program Interventions

Colonoscopies were scheduled at participating institutions (Flinders Medical Centre, Bedford Park; Repatriation General Hospital, Daw Park; and Noarlunga Hospital, Noarlunga Centre, all in South Australia) and were conducted according to best practice and accreditation requirements as they evolved during this time. Pathologic findings were characterized by colonoscopic appearance and histopathology when obtained.

The SCOOP program has included the offer of an annual fecal occult blood test in the years between colonoscopy since its inception in 2000,[6] and the scheduled colonoscopy was brought forward if the result was positive. This practice continued in the years from July 2008 to April 2019 by annual or biennial provision of a single brand of quantitative FIT (OC-Sensor, Eiken Chemical Company) applied to each of 2 stool samples. The cutoff triggering an earlier-than-scheduled colonoscopy was 20 μg Hb/g feces (100 ng/mL sample buffer) in either stool sample.

FIT kits were provided by mail, with instructions for sampling storage and return as previously described.[7] Participants were instructed to sample from 2 different stools (at least 30 minutes apart). Samples collected incorrectly were not analyzed, and a replacement kit was sent for the opportunity to repeat the test. Analysis of FIT collection tubes for Hb concentration followed the manufacturer instructions as previously described,[7] and results are expressed as μg Hb/g feces.

Outcomes

Case phenotype for a given colonoscopic examination was defined as the most advanced pathology, with the hierarchy being CRC, AA, nonadvanced adenoma (NA), and cases without neoplasia. *Cancer* was defined by the presence of invasive colorectal adenocarcinoma. *AA* was defined by the presence of adenoma with any of the following features: size $\geq$10 mm, presence of high-grade dysplasia or villous change, $\geq$3 adenomas of any size or type, sessile serrated adenoma with dysplasia, or traditional serrated adenoma. The term *advanced adenoma* refers to any of these neoplastic states, although our understanding of risk relative to adenoma number as well as the recognition of the types of serrated lesions has altered during the 12 years of observation. *Nonadvanced adenoma* consisted of any other adenoma or serrated lesion state. *Advanced neoplasia* referred to the presence of CRC or AA.

Data Modeling

FIT positivity for the entire population was estimated across a range of cutoffs up to 150 μg Hb/g and for the single-sample (specifically the first sample) or 2-sample (highest in either sample) approaches. Colonoscopy workload was determined from test result positivity rate for the entire population who returned an FIT according to selected cutoff values and sample number. Effort (the number needed to undergo colonoscopy to detect 1 case with advanced neoplasia—determined in that subset of the population who had done a 2-sample FIT in the 365 days before the colonoscopy) was calculated at selected cutoffs by dividing the number positive by the number of cases detected with the chosen phenotype. The sensitivity for CRC and AA is the number of cases in the modeling subset returning a positive FIT at a given cutoff value and sample number.

Statistical Analysis

The exact 95% confidence intervals for a finite population were calculated for each modeled outcome (sensitivity, workload, and effort) based on the size of the group and of the relevant population from which it was drawn. Analyses were performed using Stata, version 16.0 (StataCorp, College Station, TX); Excel (Microsoft, Armonk, NY), and Prism (Prism 6 for Windows, GraphPad Software, San Diego CA).

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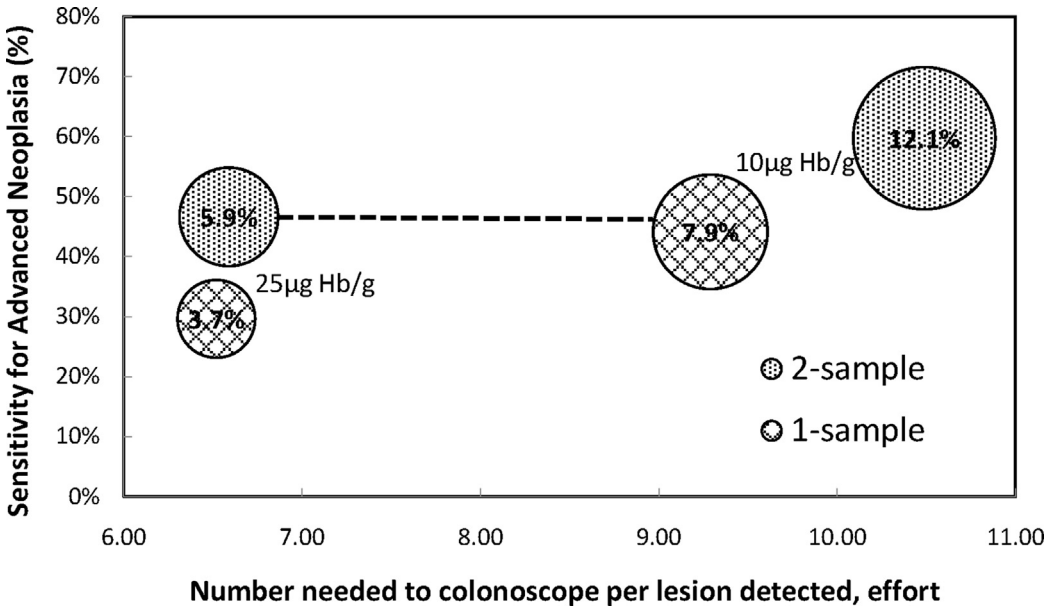

Supplementary Figure 1. Three-dimensional modeling of the relationship between colonoscopic effort (number needed undergo colonoscopy per advanced neoplasia case detected), sensitivity for advanced neoplasia, and population colonoscopy workload in selected conditions aiming for the best detection of advanced neoplasia. The pair of conditions identified as a in Figure 1 of the main manuscript (1-FIT at a cutoff 10 μg Hb/g vs 2-FIT at 25 μg Hb/g) is shown by the horizontal dashed line. Population test positivity rate (colonoscopy workload) is shown by the bubble size (rate stated in the center of each bubble). The cutoff for FIT positivity is shown adjacent to each bubble pair.

Supplementary Table 1. Modeling of the Multidimensional Relationship Between Workload and Sensitivity

Cutoff for positive result, μg Hb/g	Fecal sample number[a]	FIT population (n = 32,413) positivity rate, % (95% CI)	Tests positive (n) in patients having colonoscopy and FIT[b] (n = 4037)	Sensitivity for advanced neoplasia, % (95% CI)[b]	Number of lesions found, n[b]	Number needed to undergo colonoscopy (95% CI)[a,b]
10	1 sample: a	7.9 (7.6–8.2)	2563	44.1 (40.2–48.1)	276	9.29 (8.31–10.42): a
	2 samples	12.1 (11.7–12.5)	3923	59.7 (55.8–63.6)	374	10.49 (9.52–11.58)
20	1 sample	4.4 (4.2–4.6)	1432	34.0 (30.3–37.9)	213	6.72 (5.94–7.65)
	2 samples	7.0 (6.8–7.3)	2283	54.3 (50.3–58.3)	340	6.71 (6.09–7.43)
25	1 sample: b	3.7 (3.5–3.9)	1206	29.6 (26.0–33.3)	185	6.52 (5.71–7.49): b
	2 samples: a	5.9 (5.7–6.2)	1925	46.6 (42.7–50.6)	292	6.59 (5.93–7.36): a
40	1 sample: c	2.4 (2.3–2.6)	791	18.8 (15.9–22.1)	118	6.70 (5.68–8.00): c
	2 samples: b	4.0 (3.8–4.2)	1305	30.5 (26.9–34.2)	191	6.83 (6.00–7.83): b
80	1 sample	1.4 (1.2–1.5)	436	10.7 (8.4–13.4)	67	6.51 (5.24–8.26)
	2 samples: c	2.3 (2.1–2.5)	733	16.0 (13.2–19.1)	100	7.33 (6.12–8.90): c

NOTE. Modeling of the multidimensional relationship between workload (proportion of population requiring colonoscopy given a positive FIT result) and sensitivity (true positive rate for advanced neoplasia, namely, CRC and AA) using different combinations of selected FIT cutoffs and fecal sample number, together with effort (the number needed to undergo colonoscopy to find 1 case of advanced neoplasia).
CI, confidence interval.
[a]The letters a, b, and c refer to each of the pairs identified in Figure 1. These pairs have equivalent sensitivities.
[b]These parameters were derived from the eligible patients who also did FIT in the 365 days before colonoscopy (n = 4037); all had received colonoscopy regardless of the FIT result.