Supplementary Data

Appendix 1: Description of the 25 studies excluded from the meta-analysis of Sensitivity and Specificity.

Below we list each study excluded from our meta-analysis of the sensitivity and specificity of Hemoccult SENSA. Each study is listed only once. If a study was excluded for multiple reasons, we used the following hierarchy for assign a reason for exclusion: 1) No primary data reported (simulation study); 2) Insufficient data provided for calculation of sensitivity and specificity; 3) Evaluation of a population at high risk for colorectal cancer; 4) Study sample overlapped with another study included in our analysis.

Papers excluded because they report no primary data (simulation studies, two papers):

1. Lansdorp-Vogelaar I, Kuntz KM, Knudsen AB, Wilschut JA, Zauber AG, van Ballegooijen M. Stool DNA testing to screen for colorectal cancer in the Medicare population: a cost-effectiveness analysis. Ann Intern Med 2010;153:368-77.
2. Zauber AG, Lansdorp-Vogelaar I, Knudsen AB, Wilschut J, van Ballegooijen M, Kuntz KM. Evaluating test strategies for colorectal cancer screening: a decision analysis for the U.S. Preventive Services Task Force. Ann Intern Med 2008;149:659-69.

Papers excluded because they report insufficient data to calculate sensitivity and specificity (17 papers)

3. Tannous B, Lee-Lewandrowski E, Sharples C, Brugge W, Bigatello L, Thompson T, et al. Comparison of conventional guaiac to four immunochemical methods for fecal occult blood testing: implications for clinical practice in hospital and outpatient settings. Clin Chim Acta 2009;400:120-2.
4. Tarasi J, Dumitrescu GF, Indrei A, Plamadealla P, Trifan A, Stanciu C. Screening for colorectal cancer with fecal occult blood testing and colonoscopy: correlation of clinical data, site, size and disease's stage Jurnalul de Chirurgie 2009;5:153-64.

5. Bjerregaard NC, Tottrup A, Sorensen HT, Laurberg S. Evaluation of the Danish national strategy for selective use of colonoscopy in symptomatic outpatients without known risk factors for colorectal cancer. Scand J Gastroenterol 2007;42:228-36.
6. Smith A, Young GP, Cole SR, Bampton P. Comparison of a brush-sampling fecal immunochemical test for hemoglobin with a sensitive guaiac-based fecal occult blood test in detection of colorectal neoplasia. Cancer 2006;107:2152-9.
7. Cole SR, Young GP, Esterman A, Cadd B, Morcom J. A randomised trial of the impact of new faecal haemoglobin test technologies on population participation in screening for colorectal cancer. J Med Screen 2003;10:117-22.
8. Ko CW, Dominitz JA, Nguyen TD. Fecal occult blood testing in a general medical clinic: comparison between guaiac-based and immunochemical-based tests. Am J Med 2003; 115:111-4.
9. Rozen P, Knaani J, Samuel Z. Comparative screening with a sensitive guaiac and specific immunochemical occult blood test in an endoscopic study. Cancer 2000;89:46-52.
10. Rozen P, Knaani J, Samuel Z. Eliminating the need for dietary restrictions when using a sensitive guaiac fecal occult blood test. Dig Dis Sci 1999;44:756-60.
11. Greenberg PD, Cello JP, Rockey DC. Relationship of low-dose aspirin to GI injury and occult bleeding: a pilot study. Gastrointest Endosc 1999;50:618-22.
12. Rockey DC, Auslander A, Greenberg PD. Detection of upper gastrointestinal blood with fecal occult blood tests. Am J Gastroenterol 1999;94:344-50.
13. Sinatra MA, Young GP, St John DJ, Blake D, Ratnaike S. A study of laboratory based faecal occult blood testing in Melbourne, Australia. The Faecal Occult Blood Testing Study Group. J Gastroenterol Hepatol 1998;13:396-400.
14. Levin B, Hess K, Johnson C. Screening for colorectal cancer. A comparison of 3 fecal occult blood tests. Arch Intern Med 1997;157:970-6.
15. Foliente RL, Wise GR, Collen MJ, Abdulian JD, Chen YK. Colocare self-test versus Hemoccult II Sensa for fecal occult blood testing. Am J Gastroenterol 1995;90:2160-3.

16. Petrelli N, Michalek AM, Freedman A, Baroni M, Mink I, Rodriguez-Bigas M. Immunochemical versus guaiac occult blood stool tests: results of a community-based screening program. Surg Oncol 1994;3:27-36.
17. Petty MT, Deacon MC, Alexeyeff MA, St John DJ, Young GP. Readability and sensitivity of a new faecal occult blood test in a hospital ward environment. Comparison with an established test. Med J Aust 1992;156:420-3.
18. Castiglione G, Grazzini G, Ciatto S. Guaiac and immunochemical tests for faecal occult blood in colorectal cancer screening. Br J Cancer 1992;65:942-4.
19. Rosenthal P, Jennings MT. Comparison of fecal occult blood tests for detection of gastrointestinal bleeding in pediatric patients. Am J Gastroenterol 1992;87:1575-9.

Papers excluded because they studied a population at high risk for colorectal cancer (five papers).

20. Rozen P, Levi Z, Hazazi R, Waked A, Vilkin A, Maoz E, et al. Quantitative Colonoscopic Evaluation of Relative Efficiencies of a Quantified Immunochemical Fecal Occult Blood Test and a Sensitive Guaiac Test for Detecting Significant Colorectal Neoplasms. Gastroenterology 2009;136:A113.
21. Levi Z, Hazazi R, Rozen P, Vilkin A, Waked A, Niv Y. A quantitative immunochemical faecal occult blood test is more efficient for detecting significant colorectal neoplasia than a sensitive guaiac test. Aliment Pharmacol Ther 2006;23:1359-64.
22. Wong BC, Wong WM, Cheung KL, Tong TS, Rozen P, Young GP, et al. A sensitive guaiac faecal occult blood test is less useful than an immunochemical test for colorectal cancer screening in a Chinese population. Aliment Pharmacol Ther 2003;18:941-6.
23. Greenberg PD, Bertario L, Gnauck R, Kronborg O, Hardcastle JD, Epstein MS, et al. A prospective multicenter evaluation of new fecal occult blood tests in patients undergoing colonoscopy. Am J Gastroenterol 2000;95:1331-8.

24. St John DJ, Young GP, Alexeyeff MA, Deacon MC, Cuthbertson AM, Macrae FA, et al. Evaluation of new occult blood tests for detection of colorectal neoplasia. Gastroenterology 1993;104:1661-8.

Papers excluded because the study sample overlapped with another included study (one paper)

25. Rozen P, Knaani J, Papo N. Evaluation and comparison of an immunochemical and a guaiac faecal occult blood screening test for colorectal neoplasia. Eur J Cancer Prev 1995;4:475-81.

Appendix 2: Contribution of cohort data to estimates of sensitivity and mean sojourn time

Figure A2 demonstrates the information used to estimate the sensitivity and MST associated with Hemoccult SENSA.

Screen-positive patients (types A, B, and C) are associated with screen detection and contribute information to the first component of the likelihood, L1. False positive tests (patient type A) are identified based on six months of follow-up, and implicitly assume that all people with a positive test undergo additional work-up or within six months. Between 1997 and 2004, approximately 90% of patients with a positive FOBT had some follow-up within a year, and most underwent colonoscopy(1).Screen-detected cancers (patient types B and C) occur with probability $S \times P(\lambda_L, J_L, T)$. We assume that the probability of testing positive and then transitioning from the normal to preclinical state before disease confirmation is negligible. We treated 17 patients who were diagnosed with CRC more than six months after a positive FOBT test as having false positive tests (13 of these patients were diagnosed more than one year after a positive test). That is, we assume that had these 17 patients been assessed within 6 months of their positive FOBT, they would resemble type “A” patients rather than type “B” patients.

Screen-negative patients (types D, E, F, G, and H) are associated with symptom detection and contribute information to the second component of the likelihood, L2. Follow-up of patient types D, E, and F ends before cancer detection (the outcome is censored); These cases provide denominator information about the population at risk for developing symptom-detected (clinical) cancer. Follow-up of patient types G and H ends with clinical cancer detection. We expect yJ newly developed cancers (patient type G, and these have sojourn time that is that is less than follow-up time $1 - \exp(-\lambda(t - 0.5))$. We expect $c(1-S)/S$ missed cancers (patient type H),and these have sojourn time is greater than follow-up time $\exp(-\lambda(t - 0.5))$.

References

1. Miglioretti DL, Rutter CM, Bradford SC, et al. Improvement in the diagnostic evaluation of a positive fecal occult blood test in an integrated health care organization. Med Care 2008; 46:S91-6.

Appendix 3: Winbugs code used for primary analysis

Below we provide the algorithms and winbugs code fragments used to estimate

We estimated sensitivity (S) and mean sojourn time in the proximal and distal colorectum (mst.proxi, and mst.distal, respectively for each of the three age groups within the same model statement using a similar block of code for each each age-group, shown below for an arbitrary age group (e.g., for age group 45-50 age=50, J.proxi=1.08 per 10,000 and J.distal=2.95 per 10,000):

```
p.scr[1] <- (S*J.proxi*( exp(-age/mst.proxi) –  exp(-J.proxi*age) ) / (J.proxi-1/mst.proxi) ) /
                          (exp(-J.proxi*age) + (J.proxi*(exp(-age/mst.proxi)-exp(-J.proxi*age))/(J.proxi-1/mst.proxi)))
p.scr[2] <- (S*J.distal*( exp(-age/mst.distal) – exp(-J.distal*age) ) / (J.distal-1/mst.distal)) /
                          (exp(-J.distal*age)+(J.distal*(exp(-age/mst.distal)-exp(-J.distal*age))/(J.distal-1/mst.distal)))
p.scr[3] <- 1-p.scr[1]-p.scr[2]
can.scr[1:3] ~ dmulti(p.scr[1:3], n.scr)                                    ## L1 associated with screen-detected cancer
for(i in 1:N){
          can.int[i, 1:3] ~ dmulti(p.int[i, 1:3], py[i])                    ## L2 associated with symptom-detected cancer
      p.int[i, 1] <- ( py[i]*J.proxi*(1-exp(-(time[i]-0.5)/mst.proxi)) + can.scr[1]*((1-S)/S)*exp(-(time[i]-0.5)/mst.proxi)  )/py[i]
      p.int[i, 2] <- ( py[i]*J.distal*(1-exp(-(time[i]-0.5)/mst.distal)) + can.scr[2]*((1-S)/S)*exp(-(time[i]-0.5)/mst.distal) )/py[i]
      p.int[i, 3] <- 1-p.int[i, 1]-p.int[i, 2]
     }
    S ~ dnorm(0.748, 366.29)I(0.001, 0.999)
    mst.proxi ~ dunif(0.05, 10)
    mst.distal ~ dunif(0.05, 10)
```

For each age group, the data vector can.scr contains the number of cancers detected after a positive FOBT (proximal, distal, and none) and the matrix can.int: contains the number of cancers detected after a negative FOBT; the i-th row corresponds to the i-th year after the index FOBT with three columns for proximal, distal, and no cancers detected. The probability of screen-detected cancer, p.scr, and the probability of clinically-detected cancer after a negative test, p.int, are each calculated from data and unknown parameters