Users' Guides to the Medical Literature

XVII. How to Use Guidelines and Recommendations About Screening

Alexandra Barratt, MBBS, MPH, PhD
Les Irwig, MBBCh, PhD
Paul Glasziou, MBBS, PhD
Robert G. Cumming, MBBS, MPH, PhD
Angela Raffle, BSc (Hons), MBChB
Nicholas Hicks, MA, BMBCh
J. A. Muir Gray, CBE, MD
Gordon H. Guyatt, MD, MSc
for the Evidence-Based Medicine Working Group

CLINICAL SCENARIO

You are a family physician seeing a 47-year-old woman and her husband of the same age. They are concerned because a friend recently found out that she had bowel cancer and has urged them both to undergo screening with fecal occult blood tests (FOBTs) because, she says, prevention is much better than the cure she is now undergoing. Both your patients have no family history of bowel cancer and no change in bowel habit. They ask whether you agree that they should be screened.

You know that trials of FOBT screening have demonstrated that screening can reduce mortality from colorectal cancer (CRC), but you also recall that FOBTs can have a high false-positive rate that then requires investigation by colonoscopy. You are unsure whether screening these relatively young, asymptomatic people at average risk of bowel cancer is likely to do more good than harm. You decide to check the literature to see if there are any guidelines or recommendations about screening for CRC that might help you.

THE SEARCH

Since you know there is more than 1 randomized controlled trial (RCT), you look first for a systematic review. Your MEDLINE search (using the terms *fecal occult blood test* and *colorectal* or *colonic neoplasms* and *mass screening* and *systematic review*) produces a systematic review by Towler et al.[1] However, there may be ancillary evidence that would influence your decision about whether to recommend screening to your patient (such as the false-positive rate of the test, the adverse effects of subsequent investigation and treatment, and costs) so you also check for a practice guideline. You find the American Gastroenterological Association (AGA) guideline on CRC screening,[2] which is based on the same trials as the systematic review but also provides the additional information you were hoping to find. The full text is provided so you print off a copy to take home and read.

INTRODUCTION

When assessing a guideline or recommendation about screening you should apply the criteria suggested earlier in this series about assessment of health care interventions.[3,4] You may also consider other criteria for evaluating whether screening is worthwhile.[5-8] Sometimes screening is clearly effective, with large benefits and negligible harms, as is the case with phenylketonuria screening and screening for systolic hypertension (>160 mm Hg) among the elderly.[9] In other situations, clinicians must often weigh the benefits and harms when considering whether to screen.[10] This guide extends earlier approaches by providing a framework for assessing the methodological strength of guidelines on screening and by demonstrating the importance of weighing the benefits and harms of screening when they are closely balanced. The final decision about whether to screen is greatly influenced by the values different individuals place on each of the possible benefits and harms.

Our criteria for reviewing a guideline (or a meta-analysis) about screen-

Author Affiliations: Department of Public Health and Community Medicine, University of Sydney, Australia (Drs Barratt, Irwig, and Cumming); Department of Social and Preventive Medicine, University of Queensland, Herston, Australia (Dr Glasziou); Avon Health Authority, Bristol, England (Dr Raffle); Oxfordshire Health Authority, Oxford, England (Dr Hicks); Institute of Health Sciences, University of Oxford, England (Dr Gray); and Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario (Dr Guyatt).

The original list of members (with affiliations) appears in the first article of the series (*JAMA*. 1993; 270:2093-2095). A list of new members appears in the 10th article of the series (*JAMA*.1996;275:1435-1439). The following members of the Evidence-Based Medicine Working Group contributed to this article: Deborah Cook, MD, MSc; Lee Green, MD; Mitchell Levine, MD, MSc, FRCPC; Thomas Newman, MD; and Mark Wilson, MD.

Corresponding Author and Reprints: Gordon H. Guyatt, MD, MSc, McMaster University Health Sciences Centre, 1200 Main St W, Room 2C12, Hamilton, Ontario, Canada L8N 3Z5.

Users' Guides to the Medical Literature Section Editor: Drummond Rennie, MD, Deputy Editor (West), *JAMA*.

ing follow the Users' Guides for an article about practice guidelines (TABLE 1); in this article we will not review all the Users' Guides for guidelines, but highlight only those issues specific to screening.

TABLE 2 presents the possible consequences of screening. Some people will have true-positive test results with clinically significant disease (a^0): a proportion of this group will benefit according to the effectiveness of treatment and the severity of the detected disease. For example, children found to have phenylketonuria will experience large, long-lasting benefits. Other people will have "true"-positive test results with inconsequential disease (a^1): they may suffer harms of labeling, investigation, and treatment for a disease or risk factor that would never have affected their lives. Consider, for instance, a man in whom screening reveals low-grade prostate cancer who is destined to die of a heart attack before his prostate cancer becomes clinically manifest. He may suffer unnecessary treatment and associated adverse effects. Persons with false-positive test results (b) may suffer the harms associated with investigation of the screen-detected abnormality. Persons with false-negative test results (c^0) may experience harm if false reassurance results in delayed presentation or investigation of symptoms; some may also be angry when they discover they have a disease despite having a negative screening test result. In contrast, persons with "false"-negative test results who have inconsequential disease (c^1) are not harmed by their disease being missed because it was never destined to affect them. Persons with true-negative test results (d) may experience benefit associated with an accurate reassurance of being disease free, but may also suffer inconvenience, cost, and anxiety.

The longer the gap between possible detection and clinically important consequences, the greater the number of people in the inconsequential disease category (a^1). When screening for risk factors, very large numbers of people need to be screened and treated to prevent 1 adverse event years later,[11] and thus, most people found to have a risk factor at screening will be treated for inconsequential disease.

Table 1. Users' Guides for Guidelines and Recommendations About Screening

Are the recommendations valid?
Is there randomized controlled trial evidence that earlier intervention works?
Were the data indentified, selected, and combined in an unbiased fashion?
What are the recommendations and will they help you in caring for your patients?
What are the benefits?
What are the harms?
How do these compare in different people and with different screening strategies?
What is the impact of people's values and preferences?
What is the impact of uncertainty?
What is the cost-effectiveness?

ARE THE RECOMMENDATIONS VALID?

Is There RCT Evidence That Earlier Intervention Works?

Guidelines recommending screening are on strong ground if they are based on RCTs in which screening is compared with conventional care. In the past, many screening programs, some of them effective (such as cervical cancer screening and screening for phenylketonuria), have been implemented on the strength of observational data. When the benefits are enormous and the downsides minimal, there is no need for RCTs. More often, the benefits and harms from screening are more evenly balanced. In these situations, observational studies of screening may be misleading. Survival as measured from the time of diagnosis may be increased, not because patients live longer, but because screening lengthens the time that they know they have disease (*lead-time bias*). Patients whose disease is discovered by screening may also appear to live longer because screening tends to detect slowly progressing disease and may miss rapidly progressive disease that becomes symptomatic between screening rounds (*length-time bias*). Therefore, unless the evidence of benefit is overwhelming, RCT assessment is required.

Investigators may choose 1 of 2 designs to test the impact of a screening process. The trial may assess the entire screening process (early detection and early intervention, FIGURE 1, left), in which case people are randomized to be screened and treated if early abnormality is detected or not screened (and treated only if symptomatic disease occurs). Trials of mammographic screening have used this design.[12-14]

Alternatively, everyone may participate in screening and those with positive test results are randomized to be treated or not treated (Figure 1, right). If those who receive treatment do better, then one can conclude that early treatment has provided some benefit. Investigators usually use this design when screening detects not the disease itself, but factors that increase the risk of disease. Tests of screening programs for hypertension and high cholesterol levels have used this design.[15,16] The principles outlined in this article apply to both screening for occult disease and screening for risk factors for later disease.

Table 2. Summary of Benefits and Harms of Screening by Underlying Disease State*

	Reference Standard Results			
	Disease or Risk Factor Present			Disease or Risk Factor Absent
Screening test positive	a^0 = True positives (significant disease)	or	a^1 = "True" positives (inconsequential disease)	b = False positives
Screening test negative	c^0 = False negatives (significant disease)	or	c^1 = "False" negatives (inconsequential disease)	d = True negatives

*a^0 indicates disease or risk factor that will cause symptoms in the future (significant disease); a^1, disease or risk factor asymptomatic until death (inconsequential disease); b, false positives; c^0, missed disease that will be significant in the future; c^1, missed disease that will be inconsequential in the future; and d, true negatives. Sensitivity = a/a+c and specificity = d/b+d.

Were the Data Identified, Selected, and Combined in an Unbiased Fashion?

As for all guidelines, developers must specify the inclusion and exclusion criteria for the studies they choose to consider, conduct a comprehensive search, and assess the methodological quality of the studies they include. Towler et al[1] searched for published and unpublished trials and assessed their quality using criteria recommended by the Cochrane Collaboration. The investigators extracted data from the trials and combined them in a meta-analysis on an intention-to-screen basis.

The AGA guideline[2] on colorectal screening used explicit inclusion and exclusion criteria and a comprehensive search to identify all the RCTs of FOBT screening. The authors include a critical appraisal of the trials and conclude that the trials provide strong evidence of effectiveness, though they are limited in that they do not consider the effect of screening on health-related quality of life.

WHAT ARE THE RECOMMENDATIONS AND WILL THEY HELP YOU IN CARING FOR YOUR PATIENTS?

A good guideline about a screening program should summarize the trial evidence about benefits and present data about the harms. The guideline should then provide information about how these benefits and harms can vary in subgroups of the population and under different screening strategies.

What Are the Benefits?

What outcomes need to be measured to estimate the benefits of a screening program?

Benefits will usually be experienced by some of those with positive test results, as either a reduction in mortality or an increase in quality of life. The benefit can be estimated as an absolute risk reduction (ARR) or a relative risk reduction (RRR) in adverse outcomes. (Readers desiring a full discussion of these concepts can refer back to an earlier Users' Guide.[17]) Briefly, the ARR depends on the baseline risk of disease and thus presents a more realistic estimate of the size of the mortality benefit. The RRR, in contrast, is independent of baseline risk and can lead to a misleading impression of benefit (TABLE 3). The number of people needed to screen to prevent an adverse outcome provides another way of presenting benefit.

In addition to prevention of adverse outcomes, people may also regard knowledge of the presence of an abnormality as a benefit as in antenatal screening for Down syndrome. Another potential benefit of screening comes from reassurance afforded by a negative test result, if a person is experiencing anxiety because a family member or friend has developed the target condition or from discussion in the media. However, if the anxiety is a result of the publicity surrounding the screening program itself, we would not view anxiety reduction as a benefit.

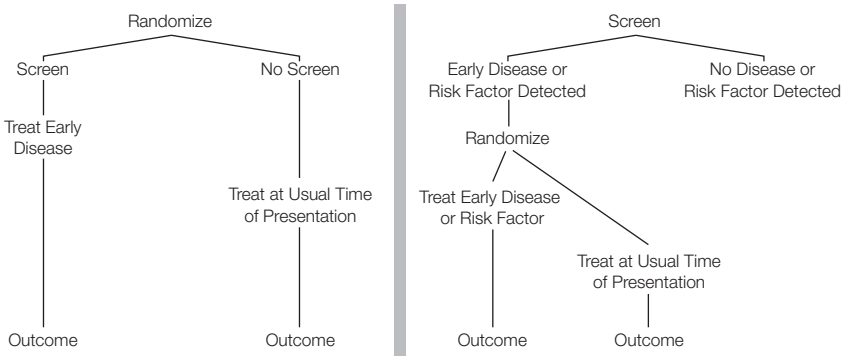
The AGA guideline reports that the RRRs from 3 trials of FOBT screening are 33% (annual screening) and 15% and 18% (biennial screening). An estimate of the uncertainty associated with these estimates (as one would get from the 95% confidence interval [CI] around a pooled RRR) would help the reader appreciate the range within which the true RRR plausibly lies. Based on a computer simulation, the AGA guideline estimates an ARR of 1330 deaths prevented per 100 000 (13.3 per 1000) people screened annually using FOBT from 50 to 85 years of age, assuming 100% participation (TABLE 4).

What Are the Harms?

Among those with positive test results, harms may include the following:

- complications arising from investigation
- adverse effects of treatment
- unnecessary treatment of persons with true-positive test results who have inconsequential disease
- adverse effects of labeling or early diagnosis
- anxiety generated by the investigations and treatment
- costs and inconvenience incurred during investigations and treatment.

Figure 1. Designs for Randomized Controlled Trials of Screening



Left, A randomized controlled trial can assess the entire screening process, in which case participants are randomized to be screened (and treated) or not screened. Right, Alternatively, everyone can participate in the screening, and those with positive results are randomized to be treated or not treated.

Table 3. Comparison of Data Presented as Relative and Absolute Risk Reductions and Number Needed to Screen With Varying Baseline Risks of Disease and Constant Relative Risk

Baseline Risk (Risk in Unscreened Group), %	Risk in Screened Group, %	Relative Risk Reduction, %	Absolute Risk Reduction, %	No. Needed to Screen
4	2	50	2	50
2	1	50	1	100
1	0.5	50	0.5	200
0.1	0.05	50	0.05	2000

Table 4. Clinical Consequences for 1000 People Entering a Program of Annual Fecal Occult Blood Test Screening for Colorectal Cancer at Age 50 Years and Remaining in the Program Until 85 Years of Age or Death*

Clinical Consequences	No.
Harms	
Screening tests	27 030
Diagnostic evaluations (by colonoscopy)	2263
False-positive screening tests	2158
Deaths due to colonoscopy complications	0.5
Bowel perforations from colonoscopy	3.0
Major bleeding episodes from colonoscopy	7.4
Minor complications from colonoscopy	7.7
Benefits	
Deaths averted	13.3
Years of life saved	123.3
Years of life gained per person whose cancer death was prevented	9.3

*Adapted from Winawer et al.[2]

The AGA guideline reports that of the patients who do not have CRC, 8% to 10% will have false-positive test results (specificity, 90%-92% using rehydrated slides). In the trials, only 2% to 6% of those with positive test results actually had colon cancer (positive predictive value, 2%-6%). Thus, of every 100 screening participants with a positive test result, only 2 to 6 will have cancer, but all 100 will be exposed to colonoscopy and its attendant risks (Table 4). While the colonoscopies will reveal few cancers, they will show many polyps (25% of people aged 50 years or older have polyps, some of which will be judged to need removal depending on the size of the polyp). Part of the benefit of screening will come from removal of the small proportion of polyps that would have progressed to invasive cancer. Part of the harm of screening will come from regular colonoscopies that are recommended for people who have had a benign or inconsequential polyp removed.

Among those with negative test results, harms may include the following:

- anxiety generated by the screening test (waiting for result)
- false reassurance (and delayed presentation of symptomatic disease later)
- costs and inconvenience incurred during the screening test.

Of those who have cancer, FOBT screening using rehydrated slides will correctly identify 90% and miss the other 10% (sensitivity of 90%), according to the AGA guideline. Those who present with symptoms after a false-negative screen may experience a sense of anger and betrayal that they would not suffer in the absence of a screening program.

Using the computer simulation, the AGA guideline presents data on the frequency of some of these harms. These data are summarized in Table 4 for 1000 people participating in annual screening by FOBT from 50 to 85 years of age. The model assumes those who test positive have a colonoscopy.

We now know the magnitude of both benefits and harms (as presented in Table 4). This balance sheet tells us that screening 1000 people annually with FOBT from 50 years of age will prevent 13.3 deaths from CRC, but will cause 0.5 deaths from the complications of investigation and surgery. There will also be 10.4 major complications (perforations and major bleeding episodes) and 7.7 minor complications. The authors provide no data on anxiety, but we could assume that some people will feel anxious prior to colonoscopy. FIGURE 2 presents these data as a flow diagram.

These data assume that the screening programs will deliver the same magnitude of benefit and harms as found in RCTs; this will be true only if the program is delivered to the same standard of quality as in the trials. Otherwise, benefits will be smaller and the harms greater.

How Do Benefits and Harms Compare in Different People and With Different Screening Strategies?

The AGA guideline recommends that people at average risk and older than 50 years of age be offered screening for CRC. The guideline discusses several screening strategies (FOBT, flexible sigmoidoscopy, barium enema, and colonoscopy) and, in relation to FOBT, recommends offering annual screening. The magnitude of benefits and harms will vary in different patients and under different screening strategies, as the following discussion reveals.

Risk of Disease. Assuming that the RRR is constant over a broad range of risk of disease, benefits will be greater for people at higher risk of disease. For example, mortality from CRC rises with age, and the mortality benefit achieved by screening rises accordingly (FIGURE 3, top). But the life years lost in the population to CRC are related both to the age at which mortality is highest and the length of life still available. Thus, the number of life years that can be saved by CRC screening increases with age to about 75 years and then decreases again as life expectancy declines (Figure 3, bottom). The number of deaths averted by screening over 10 years for those aged 40, 50, and 60 years at first screening (0.2, 1.0, and 2.4, respectively, per 1000 people[1]) reflects these differences. Because of a greater benefit, it may be rational for a 60-year-old person to decide screening is worthwhile, while a 40-year-old person (or 80 years old) with smaller potential benefit might decide it is not worthwhile.

Risk of disease, and therefore benefits from screening, may be increased by other factors, such as a family history. The AGA guideline reports that people with 1 or more first-degree relatives (parent, sibling, child) with CRC, but without one of the specific genetic syndromes, have approximately twice the risk of developing CRC as average-risk individuals without a family history. This means that for people aged 40 years who have a first-degree relative with CRC, the incidence of CRC is comparable to that for people aged 50 years without a family history. The guideline also notes that within each age group, the risk is greatest in those whose relatives developed cancer at a younger age.

Screening Interval. As the screening interval is shortened, the effectiveness of a screening program will tend to improve, although there is a limit to the amount of improvement that is pos-

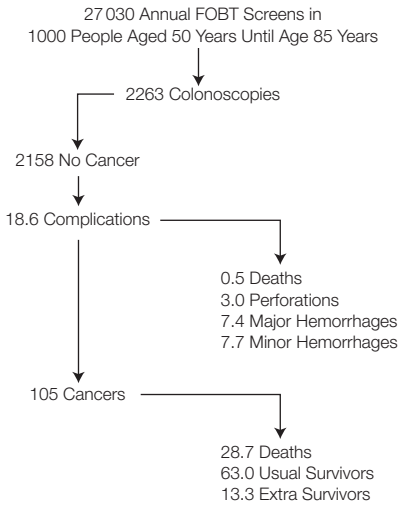
sible. For example, screening twice as often could theoretically double the relative mortality reduction obtainable by screening, but in practice, the effect is usually much less. Cervical cancer screening may, for instance, reduce the incidence of invasive cervical cancer by 64%, 84%, and 94% if screening is conducted at 10-year, 5-year, and annual intervals, respectively.[18]

The frequency of harms will also increase with more frequent screening, potentially directly in proportion to the frequency of screening. Thus, we will see diminishing marginal return as the screening interval is shortened. Ultimately, the marginal harms will outweigh the marginal benefit of further reductions in the screening interval.

Test Characteristics. If the sensitivity of a new test is greater than the test used in the trials and is detecting significant disease earlier, the benefit of screening will increase. But it may be that the new, apparently more sensitive, test is detecting more cases of inconsequential disease (for example, by detecting more low-grade prostate cancers or more low-grade cervical epithelial abnormalities[19]), which will increase the harms. On the other hand, if specificity is improved and testing produces fewer false-positive results, net benefit will increase and the test may now be useful in groups in which the old test was not.

Ideally, clinicians would look to RCTs of the new test compared with the old test. However, new tests often appear in profusion, and randomized trials are expensive and often only interpretable after long follow-up. Being pragmatic, we will usually need to accept that the trials have shown that earlier detection works and a comparison of a new vs the old test only needs to examine test characteristics. Returning to CRC screening, since we have RCT data of mortality reduction, we may assume that earlier detection using other methods such as flexible sigmoidoscopy will also reduce mortality from CRC even though there are no published reports of RCTs of screening with flexible sigmoidoscopy.

Figure 2. Flow Diagram of the Clinical Consequences for 1000 People Entering a Program of Annual Fecal Occult Blood Test (FOBT) Screening for Colorectal Cancer (CRC) at Age 50 Years and Remaining in the Program Until 85 Years of Age or Death



Usual survivors are those who would have survived with or without screening. Extra survivors are those in whom the earlier detection of cancer averts death. Adapted from Winawer et al.[2]

What Is the Impact of People's Values and Preferences?

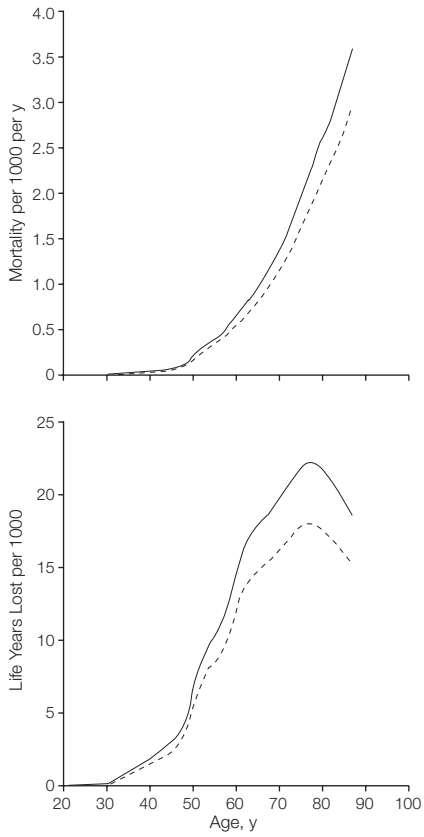
People will value benefits and harms of screening differently. For example, pregnant women who are considering screening for Down syndrome may make different choices depending on the value they place on having a Down syndrome baby vs the risk of iatrogenic abortion from amniocentesis.[20]

Individuals who choose to participate in screening programs are benefiting (in their view) from screening, and other individuals are benefiting (in their view) from not participating. Individuals can only make the right choice for themselves if they have access to high-quality information about the benefits and harms of screening and are able to weigh that information. This probably will require much better educational materials and decision support materials; some examples are already available.[21,22]

What Is the Impact of Uncertainty Associated With the Evidence?

There is always uncertainty about the benefits and harms of screening. The

Figure 3. Mortality From Colorectal Cancer and Years of Life Lost Due to Colorectal Cancer With and Without Screening



Top, Mortality from colorectal cancer. Bottom, Life years lost due to colorectal cancer. Broken lines indicate with screening, and solid lines, without screening. Data from Towler et al.[1]

95% CIs around the magnitude of each benefit and harm provides an indication of the amount of uncertainty in each estimate. Where sample size is limited, the CIs will be wide and clinicians should alert potential screening participants that the magnitude of the benefit or harm could be considerably smaller or greater than the point estimate.

What Is the Cost-effectiveness?

While clinicians will be most interested in the balance of benefits and harms for their individual patients, policymakers must consider issues of cost-effectiveness and local resources in their decisions. Clinicians can look to previous Users' Guides to help them

evaluate studies addressing these economic issues.[23,24]

The AGA guideline reports that the estimated cost-effectiveness of FOBT screening is approximately $10 000 per life year gained among people older than 50 years (although, like the absolute size of the benefit, it will vary with risk of disease). The AGA guideline also notes that all CRC screening strategies examined (FOBT, flexible sigmoidoscopy, barium enema, colonoscopy) cost less than $20 000 per life year saved.

These cost-effectiveness ratios are within the range of what is currently paid in some countries for the benefits of other screening programs such as mammographic screening for women aged 50 to 69 years (estimated at $21 400 per life year saved[25]), ultrasound screening for carotid stenosis (incremental cost per quality-adjusted life year gained is estimated at $39 495[26]) and ultrasound screening for abdominal aortic aneurysm in men aged 60 to 80 years (estimated $41 550 per life year gained[27]).

RESOLUTION OF THE SCENARIO

The guideline should quantify the benefit of screening according to age so you can inform your patients as accurately as possible about the benefits of screening for them. The AGA guideline does not provide age-specific mortality reductions attributable to screening; therefore, you cannot easily quantify the benefit for your patients. From the guideline, all you could say is that screening a group of 1000 people with FOBT beginning at 50 years of age and continuing annually to 85 years of age will avert about 13 deaths from CRC. However, we know from the systematic review by Towler et al[1] that the mortality benefit for people between 40 and 50 years of age is about 0.2 to 1.0 deaths averted over 10 years per 1000 people screened. Next you could outline the potential harms of screening. As noted earlier, the harms are mostly related to the colonoscopy. According to the AGA guideline, the risks of colonoscopy are about 0.1 to 0.3 per 1000 for death, and 1 to 3 per 1000 for perforation and hemorrhage. In addition, there would also be issues of cost, inconvenience, and anxiety.

It is up to your patients to weigh whether the benefit of reduced risk of death from CRC is worth the risks. If they feel unable to do this, then you could consider helping them to clarify their values about the possible outcomes. For example, if they are not bothered by the prospect of a colonoscopy, they would probably choose to be screened. But if either of them places a high value on avoiding colonoscopy now, he or she may prefer to reconsider screening in a few years' time when the benefits will be greater.

REFERENCES

1. Towler B, Irwig L, Glasziou P, et al. A systematic review of the effects of screening for colorectal cancer using the faecal occult blood test, Hemoccult. *BMJ.* 1998;317:559-565.
2. Winawer SJ, Fletcher RH, Millar L, et al. Colorectal cancer screening: clinical guidelines and rationale. *Gastroenterology.* 1997;112:594-642.
3. Hayward RSA, Wilson MC, Tunis SR, et al, for the Evidence-Based Medicine Working Group. Users' guides to the medical literature, VIII: how to use clinical practice guidelines, A: are the recommendations valid? *JAMA.* 1995;274:570-574.
4. Wilson MC, Hayward RS, Tunis SR, et al, for the Evidence-Based Medicine Working Group. Users' guides to the medical literature, VIII: how to use clinical practice guidelines, B: what are the recommendations and will they help you in caring for your patients? *JAMA.* 1995;274:1630-1632.
5. Wilson JMG, Jungner G. *Principles and Practice of Screening for Disease.* Geneva, Switzerland: World Health Organization; 1968.
6. Muir Gray JA. *Evidence-Based Healthcare.* New York, NY: Churchill Livingstone; 1997.
7. Sackett DL, Haynes RB, Tugwell P. *Clinical Epidemiology: A Basic Science for Clinical Medicine.* 2nd ed. Boston, Mass: Little Brown & Co; 1991.
8. Welch HG, Black WC. Evaluating randomized trials of screening. *J Gen Intern Med.* 1997;12:118-124.
9. SHEP Co-operative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA.* 1991;265:3255-3264.
10. Eddy DM. Comparing benefits and harms: the balance sheet. *JAMA.* 1990;263:2493, 2498, 2501, 2505.
11. Khaw KT, Rose G. Cholesterol screening programmes: how much benefit? *BMJ.* 1989;299:606-607.
12. Andersson I, Aspegren K, Janzon L, et al. Mammographic screening and mortality from breast cancer: the Malmo mammographic screening trial. *BMJ.* 1988;297:943-948.
13. Tabar L, Fagerberg G, Duffy S, et al. The Swedish two county trial of mammographic screening for breast cancer: recent results and calculation of benefit. *J Epidemiol Commun Health.* 1989;43:107-114.
14. Roberts MM, Alexander FE, Anderson TJ, et al. Edinburgh trial of screening for breast cancer: mortality at seven years. *Lancet.* 1990;335:241-246.
15. Multiple Risk Factor Intervention Trial Research Group. Multiple Risk Factor Intervention Trial: risk factor changes and mortality results. *JAMA.* 1982;248:1465-1477.
16. Frick MH, Elo E, Haapa K, et al. Helsinki Heart Study: primary prevention trial with gemfibrizil in middle-aged men with dyslipidemia. *N Engl J Med.* 1987;317:1237-1245.
17. Guyatt GH, Sackett DL, Cook DJ, for the Evidence-Based Medicine Working Group. Users' guides to the medical literature, II: how to use an article about therapy or prevention, B: what were the results and will they help me in caring for my patients? *JAMA.* 1994;271:59-63.
18. IARC Working Group on Evaluation of Cervical Cancer Screening Programmes. Screening for squamous cervical cancer: duration of low risk after negative results of cervical cytology and its implication for screening policies. *BMJ.* 1986;293:659-664.
19. Raffle AE. New tests in cervical screening. *Lancet.* 1998;351:297.
20. Fletcher J, Hicks NR, Kay JDS, Boyd PA. Using decision analysis to compare policies for antenatal screening for Down's syndrome. *BMJ.* 1995;311:351-356.
21. Wolf A, Nasser J, Wolf AM, Schorling JB. The impact of informed consent on patient interest in prostate-specific antigen screening. *Arch Intern Med.* 1996;156:1333-1336.
22. Flood AB, Wennberg JE, Nease RF, et al. The importance of patient preference in the decision to screen for prostate cancer. *J Gen Intern Med.* 1996;11:342-349.
23. Drummond MF, Richardson WS, O'Brien BJ, Levine M, Heyland D, for the Evidence-Based Medicine Working Group. Users' guides to the medical literature, XIII: how to use an article on economic analysis of clinical practice, A: are the results of the study valid? *JAMA.* 1997;277:1552-1557.
24. O'Brien BJ, Heyland D, Richardson WS, Levine M, Drummond MF, for the Evidence-Based Medicine Working Group. Users' guides to the medical literature, XIII: how to use an article on economic analysis of clinical practice, B: what are the results and will they help me in caring for my patients? *JAMA.* 1997;277:1802-1806.
25. Salzmann P, Kerlikowske K, Phillips K. Cost-effectiveness of extending screening mammography guidelines to include women 40-49 years. *Ann Intern Med.* 1997;127:955-965.
26. Yin D. Carpenter JP. Cost-effectiveness of screening for asymptomatic carotid stenosis. *J Vasc Surg.* 1998;27:245-255.
27. Frame PS, Fryback DG, Patterson C. Screening for abdominal aortic aneurysm in men ages 60 to 80 years: a cost-effectiveness analysis. *Ann Intern Med.* 1993;119:411-416.