22.3

ADVANCED TOPICS IN MOVING FROM EVIDENCE TO ACTION

MOVING FROM EVIDENCE TO ACTION: RECOMMENDATIONS ABOUT SCREENING

Alexandra Barratt, Les Irwig, Paul Glasziou, Robert Cumming, Angela Raffle, Nicholas Hicks, J. A. Muir Gray, and Gordon Guyatt

IN THIS CHAPTER:

CLINICAL SCENARIO

Should a 47-Year-Old Couple Undergo Colon Cancer Screening?

You are a primary care physician treating a 47-year-old woman and her husband of the same age. They are concerned because a friend of theirs recently received news she had colon 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.

Neither of these patients has a family history of colon cancer or a 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, which then necessitates investigation by colonoscopy. You are unsure whether screening these relatively young, asymptomatic people with no risk factors for colon cancer is likely to do more good than harm. You decide to check the literature to see whether there are any guidelines or recommendations about screening for CRC that might help you respond to their question.

FINDING THE EVIDENCE

You log on and use PubMed to search MEDLINE using the terms "colorectal neoplasms AND mass screening" and limit your search to practice guidelines and English language. Your search retrieves 36 citations, including 2 recent citations that look especially promising. These are clinical guidelines by the US Preventive Services Taskforce (USPSTF)[1] and the American Gastroenterological Association (AGA).[2] Both are available online. You obtain the full version of the USPSTF guideline, including the *systematic review* on which the recommendations are based, from their Web site,[3] in addition to the AGA guideline. A quick scan of these articles reveals that the USPSTF guideline has more about the adverse effects of screening that is of particular interest, so you first look at these guidelines.

CONSEQUENCES OF SCREENING

The best way to think about screening is as a therapeutic intervention. Doing so immediately clarifies the *evidence* required to support a policy of screening: randomized trials examining the effect of screening vs no screening on patient-important outcomes.[4-6] In this chapter, we probe specific issues introduced in Chapter 21, How to Use a Patient Management Recommendation, focusing on those that are specific to screening (Table 22.3-1).

Table 22.3-2 presents the possible consequences of screening. Some people will have true-positive results with clinically important disease (cell a); some of this group—the proportion depending on the effectiveness of treatment and the severity of the detected disease—will benefit from screening. For instance, children found on screening to have phenylketonuria will experience large, long-lasting benefits because there is effective treatment for asymptomatic disease, and it is better than waiting and treating the disease once symptoms develop. If no effective treatment for asymptomatic disease is available or knowing about the disease does not otherwise provide benefit, screening is not sensible.

Other people will have true-positive results, but their disease will be clinically irrelevant (overdetection) (cell b). These people meet pathologic criteria, but their

TABLE 22.3-1

Users' Guides for Recommendations About Screening

Are the recommendations valid?

- Is there randomized trial evidence that the intervention benefits people with asymptomatic disease?
- Were the data identified, selected, and combined in an unbiased fashion?

What are the recommendations and will they help you in caring for patients?

- What are the benefits?
- What are the harms?
- How do benefits and harms compare in different people and with different screening strategies?
- What is the effect of individuals' values and preferences?
- What is the effect of uncertainty associated with the evidence?
- What is the cost-effectiveness?

TABLE 22.3-2

Summary of Benefits and Harms of Screening by Underlying Disease State

Screening Test Result	Reference Standard Results: Disease or Risk Factor Present		Reference Standard Results: Disease or Risk Factor Absent
Positive	True positives[a]	"True" positives (clinically irrelevant disease)[b]	False positives[c]
Negative	False negatives[d]	"False" negatives (clinically irrelevant disease)[e]	True negatives[f]

[a]Disease or risk factor that will cause symptoms in the future.
[b]Disease or risk factor asymptomatic until death (clinically irrelevant disease).
[c]False-positive results.
[d]Missed disease that will be symptomatic in the future.
[e]Missed disease that will be clinically irrelevant in the future.
[f]True-negative results.

Sensitivity = a + b / a + b + e + d; specificity = f / c + f.

disease is destined not to become clinically relevant within their lifetime. Consider, for instance, a man in whom screening reveals low-grade prostate cancer but who dies some years later from coronary artery disease before his prostate cancer becomes clinically manifest. This man has had to cope with a cancer diagnosis and may have had treatment and adverse effects from that treatment. Thus, these individuals may experience labeling, investigation, and treatment for a disease or *risk factor* that, without screening, would not have affected their lives.

Overdetection and overtreatment may turn out to be the most important downside of screening for some conditions. For example, approximately 50% of the prostate cancers found by screening in men aged 50-70 would have remained clinically silent in the men's lifetimes.[7] In breast cancer screening, detection of some, perhaps even the majority, of ductal carcinoma in situ (DCIS) may be overdetection[8]; estimates of the extent of overdetection of invasive breast cancer range widely from 2% to 30%.[9-11]

People with *false positive* results (cell c) may be adversely affected by the *risks* associated with investigation of the screen-detected abnormality, such as the complications of colonoscopy after a positive FOBT result. People with *false negative* results of clinically important disease (cell d) may experience *harm* if false reassurance results in delayed presentation or investigation of symptoms. Screened patients may feel emotional distress and anger if they discover they have disease despite having negative screening test results.

By contrast, patients with false-negative results with clinically irrelevant disease (cell e) are not harmed by their disease being missed because it was never destined to affect them. Patients with *true negative* results (cell f) may experience benefit associated with an accurate reassurance of being disease free, but they may also experience inconvenience, cost, and anxiety.

The longer the gap between possible detection and patient-important consequences, the greater the number of people who may experience overdetection (cell b). When screening for risk factors (such as high blood pressure or elevated cholesterol level), one must screen and treat very large numbers of people to prevent 1 adverse event years later.[12]

ARE THE RECOMMENDATIONS VALID?

Is There Randomized Trial Evidence That the Intervention Benefits People With Asymptomatic Disease?

Guidelines recommending screening are on strong ground if they are based on *randomized controlled trials* (*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 are minimal, there is no need for randomized trials. More often, however, the benefits and risks from screening are finely balanced, and *observational studies* of screening may be misleading.

There are a number of reasons observational studies 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 also may appear to do better or live longer than people whose disease presents clinically with symptoms because screening tends to detect disease that is destined to progress slowly and which therefore has a good prognosis (length time bias). Length time bias occurs when rapidly progressing disease becomes symptomatic before the next scheduled screening test and so is not detected by screening, whereas slowly progressing disease is still asymptomatic and detectable by screening at the next screening round. This adds an additional bias to studies that compare the prognosis in tumors detected by screening to those not detected by screening. These considerations dictate performing randomized trial assessment of the therapy that patients will receive before implementation of screening programs.

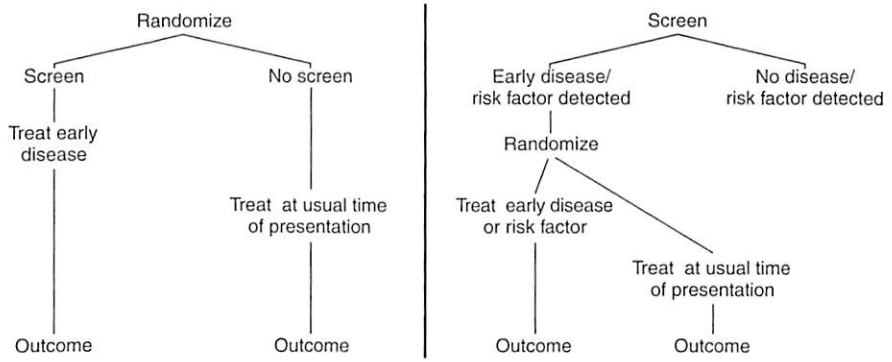
Study Designs for Randomized Trials of Screening

Investigators may choose one of 2 study designs to test the effect of screening. Investigators may assess the entire screening process (early detection and early intervention; see Figure 22.3-1), in which case they randomize people 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.[13]

Alternatively, all participants may undergo screening, and those with positive results are randomized to be treated or not treated (Figure 22.3-1). If those who receive treatment do get better, then one can conclude that early treatment has provided

FIGURE 22.3-1

Designs for Randomized Controlled Trials of Screening



Reproduced from Barratt et al,[4] with permission from *JAMA*.

benefit. Investigators usually use this study 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 level have used this design.[14] The principles outlined in this chapter apply to both of the study designs (Figure 22.3-1) used in addressing screening issues.

Regardless of which design investigators use, a successful outcome of screening depends on optimal, or at least appropriate, application of testing and treatment that follows a positive screening test result.

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

As is true for all guidelines, developers must specify the inclusion criteria and exclusion criteria for the studies they choose to consider, conduct a comprehensive search, and assess the methodologic quality of the studies they include.

USING THE GUIDES

Both guides consider CRC screening using a range of tests, including FOBT. The USPSTF provides details of the search strategies used, inclusion and exclusion criteria, studies found, and the quality of evidence each study provides. The AGA guideline updates an earlier guideline and gives limited information about its *review* process. Three randomized trials of screening using FOBT were identified by both guides, providing high-quality-level evidence of clinically and statistically significant reductions in the risk of death from CRC. Both also include evidence from a range of other studies addressing issues of test accuracy and, in the guideline by the USPSTF, adverse effects of screening. The AGA guideline also provides recommendations for screening people with a familial or inherited risk of CRC.

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

Recommendations about a screening program should include evidence about benefits and risks; for example, in a "balance sheet."[15] Ideally, they should also provide information about how these benefits and risks can vary in subgroups of the population and under different screening strategies.

What Are the Benefits?

What outcomes must investigators measure to estimate the benefits of a screening program? If treatment is effective, some of those who test positive will experience a reduction in mortality or an increase in quality of life. One can estimate the benefit as an absolute risk reduction or a *relative risk reduction* (*RRR*) in adverse outcomes (see Chapter 7, Does Treatment Lower Risk? Understanding the Results). The *number of people needed to screen* (*NNS*) to prevent an adverse outcome provides another way of presenting benefit (see Chapter 7, Does Treatment Lower Risk? Understanding the Results). When the benefit is a reduction in mortality, we would like to see a reduction in both disease-specific and total mortality (ie, mortality from any and all possible causes). Because the target condition is typically only one of many causes of death, however, even important reductions in disease-specific mortality are unlikely to result in statistically significant reductions in total mortality. In some conditions for which mortality is high, it may be reasonable to expect a reduction in total mortality, as well as in disease-specific mortality. For the most part, however, we will have to be satisfied with demonstrated reductions in disease-specific mortality only, although it is reassuring if investigators present data showing no increase in total mortality.

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 the 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 popular media. However, a test can increase rather than decrease a person's self-perception as being at risk. In instances in which anxiety is a result of the publicity surrounding the screening program itself, we would not view anxiety reduction as a benefit.

The USPSTF reports results from the 3 randomized trials of FOBT screening that have published outcome results. All used Hemoccult tests (Beckman Coulter, Fullerton, CA). Two European trials (1 in England and 1 in Denmark) provided biennial screening and reported RRRs of 15% and 18%, respectively.[16,17] The third trial (in Minnesota) evaluated annual and biennial screening and found RRRs of 33% and 21%, respectively, for these strategies.[18,19] A meta-analysis by Towler et al[20] (cited by the USPSTF) provides a pooled RRR of 23% from biennial screening; this estimate is adjusted for compliance, so it provides an estimate of the effect among people who actually attend for screening regularly.

What Are the Harms?

Among those who test positive, adverse consequences may include

- complications arising from investigation (screening test);
- adverse effects of treatment;
- unnecessary (over-)treatment of persons having true-positive results (clinically irrelevant disease, overdetection);
- adverse effects of labeling and early diagnosis;
- anxiety generated by the investigations and treatment; and
- costs and inconvenience incurred during investigations and treatment.

The USPSTF review observed that test accuracy data are conventionally reported for a test at a single point, whereas for a screening program, cumulative test-positive data over time are more relevant. The colonoscopy rate was about 5% in the European trials during 8 to 10 years but much higher (38% for annual screening and 28% for biennial screening) in the Minnesota trial. The Minnesota study primarily used rehydrated tests that increase the sensitivity but also increase the false-positive rate. As a result, the AGA guideline recommends using unhydrated tests, whereas the USPSTF just states the tradeoff.

For the European trials, which used unrehydrated tests in biennial screening, the false-positive rate was about 2% in the initial screening round and about 1% in subsequent rounds. Because the target condition is relatively rare (and the pretest probability is low), many of the positive results will be false positives. Of those who tested positive, only 2.2% in the Minnesota trial and 8% to 18% in the 2 European studies proved to have CRC.

Adverse effects of colonoscopy are one of the main risks of CRC screening. Data from the UK trial showed that 7 (0.5%) of 1474 people undergoing colonoscopy experienced a major complication (5 perforations, 1 hemorrhage, and 1 snare entrapment; 6 of 7 people required surgical intervention).[21] More recently, results of the first round of a demonstration pilot of screening for CRC in the United Kingdom found that 0.24% of patients were admitted for overnight observation because of bleeding or abdominal pain.[22] The USPSTF review reports data from 16 studies of the complications of colonoscopy. Estimates range from 0% to 0.7% for perforation, from 0% to 2.1% for bleeding, and from 0% to 0.06% for death.[3]

To date, there are few data published on overdetection of invasive cancer in bowel cancer screening.[21] Many people have polyps found (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 polyp removal but who were destined to never develop CRC. As noted earlier among those who test negative, adverse consequences may include false reassurance and delayed presentation of later symptomatic disease. FOBT screening will detect only about 50% of the cancers that occur in a population of regularly screened people.[3] Thus, the interval cancer rate (which includes both missed cancers and cancers that develop de novo in the screening interval) is about 50%. There are also the costs, inconvenience, and anxiety generated by just having the screening test, even for those who receive a normal test result.

Balancing Benefits and Harms

Neither the USPSTF report nor the AGA guideline reports the data in a user-friendly format, such as outcomes per 10000 people aged 40, 50, and 60 years during 10 years who are screened or not screened.[23] We can, however, use the data to construct a simple balance sheet (see Table 22.3-3).[15] To start with, we need to know what the cumulative 10-year risk of death from CRC is without screening. Data on cancer mortality rates are available through a large American cancer registry (Surveillance, Epidemiology and End Results [SEER]).[24] Currently, the 10-year cumulative mortality for men aged 40, 50, and 60 years is approximately 7, 24, and 65 per 10000, respectively. For women, the rates are 5, 16, and 39 per 10000, respectively. Among people who are regularly screened, we expect the risk of death from CRC to be reduced by 23%.[20] So, with screening, the mortality rates would be approximately 5, 19, and 50 per 10000 for men. For women who are screened, the rates will be 4, 12, and 30 per 10000. We can enter these data into the top row of our balance sheet.

Using the test positivity rates reported in the European trials (2% initial round and 1% each subsequent round), we can estimate that about 6%, or 600 of 10000 people, will have a positive test result during 5 rounds and thus receive a recommendation for colonoscopy. We can add this estimate to our balance sheet (Table 22.3-3, row 2). Finally, we add estimates of the number of adverse events from colonoscopy to our balance sheet (Table 22.2-3, row 3). We could use the UK trial data, which are about midrange in the estimates provided by the USPSTF report (ie, a total adverse event rate of 0.5%). So of the 600 people having colonoscopy, we would expect 3 people to have a serious event (Table 22.3-3).

Simple and approximate, the balance sheet provides perspective on the benefits and harms of CRC screening. Unfortunately, we have no data on the risk of overdetection or on anxiety and effect on quality of life. This balance sheet tells us that screening 10000 men biennially with FOBT from age 50 years will prevent approximately 5 deaths from CRC during 10 years but will lead to about 600 colonoscopies and 3 major colonoscopy complications during the same period. The balance of benefits vs harms becomes more favorable with increasing age.

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 that in the trials. Otherwise, benefits will be smaller and the harms will be greater.

Balance Sheet of Outcomes During 10 Years of Bowel Cancer Screening per 10000 People Aged 40, 50, and 60 Years Who Accept or Decline Biennial Screening[a]

	40-Year-Olds		50-Year-Olds		60-Year-Olds	
	Screen (10000)	No Screen (10000)	Screen (10000)	No Screen (10000)	Screen (10000)	No Screen (10000)
Deaths caused by CRC						
Men	5	7	19	24	50	65
Women	4	5	12	16	30	39
Positive screening test results leading to recommendation for colonoscopy	600		600		600	
Major adverse effects of colonoscopy (eg, perforation, hemorrhage)	3		3		3	

Abbreviation: CRC, colorectal cancer.

[a]Based on data from SEER[24] and US Life Tables.[25]

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

The USPSTF review[3] strongly recommends that CRC screening be offered to all people older than 50 years. The review discusses several screening strategies: FOBT, colonoscopy, flexible sigmoidoscopy, and double-contrast barium enema. The magnitude of benefits and harms will vary in different patients and with different screening strategies, as the following discussion reveals. The benefits of screening are experienced at some point in the future, whereas harms may be experienced at any time, including immediately after the first screening.

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 increases with age, and the mortality benefit achieved by screening increases accordingly (Figure 22.3-2). But the life-years lost 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 80 years and then decreases again as life expectancy declines (Figure 22.3-2). Because of a greater benefit, it may be rational for a person aged 60 years to decide

FIGURE 22.3-2A

Mortality Rates for Colorectal Cancer

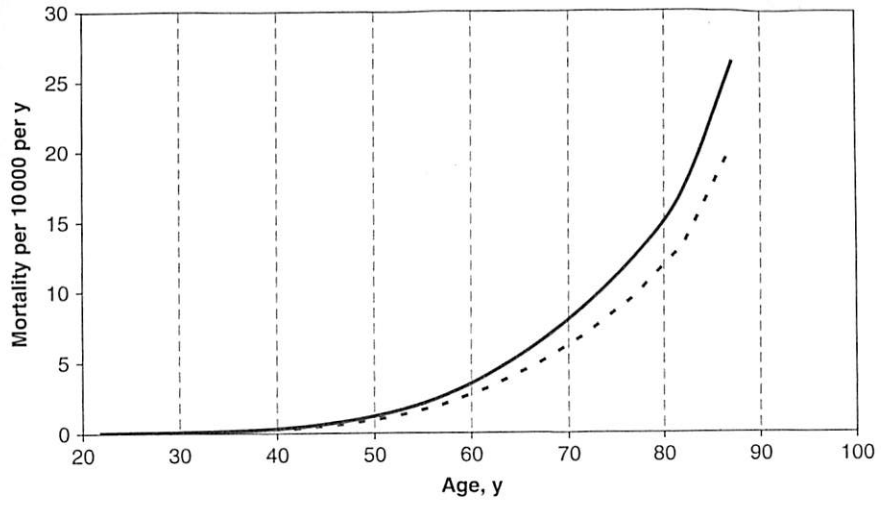
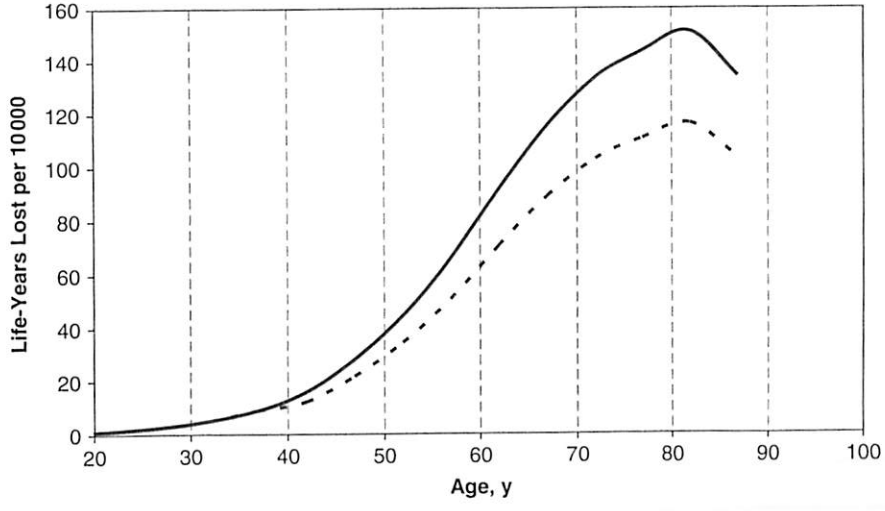


FIGURE 22.3-2B

Life-years Lost to Colorectal Cancer



A and B, The solid lines represent disease-specific mortality from colorectal cancer and life-years lost as a result of colorectal-cancer deaths in patients who do not undergo screening. The dashed line represents results in patients who undergo screening.

Data based on SEER[24] and US Life Tables.[25]

screening is worthwhile, whereas a person aged 40 years with smaller potential benefit might decide it is not worthwhile.

Factors such as a family history may increase risk of disease and therefore benefits from screening. The USPSTF focuses only on average-risk people, but the AGA guideline[2] reports that people having 1 affected first-degree relative approximately doubles colon cancer risk and having more than 1 affected first-degree relative increases risk by approximately 4-fold. These people would derive approximately 2 and 4 times, respectively, as great a benefit from screening as average-risk people.

Screening Interval

As the screening interval gets shorter, the effectiveness of a screening program will tend to improve. For example, screening twice as often could theoretically double the relative mortality reduction obtainable by screening. In practice, however, the effect is usually much less. Cervical cancer screening, for instance, may reduce the incidence of invasive cervical cancer by 64%, 84%, and 94% if screening is conducted at 10-, 5-, and 1-year intervals, respectively.[26] The frequency of harms also will 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. For example, in our balance sheet, if patients undergo screening annually, the benefit would be a little larger, but the number of colonoscopies and adverse events from colonoscopies would be approximately doubled.

Test Characteristics

If the sensitivity of a new test is greater than that of the test used in the trials and if it is detecting significant disease earlier, the benefit of screening will increase. But it may be that the new and apparently more sensitive test is detecting more cases of inconsequential disease (eg, by detecting more low-grade prostate cancers or more low-grade cervical epithelial abnormalities[27]), which will increase the potential for harm. 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 as useful.[28]

What Is the Effect of Values and Preferences?

How people value the benefits and harms of screening varies. For example, couples considering fetal screening for Down syndrome may make different choices, depending on the value they place on having a child with Down syndrome vs the risk of iatrogenic abortion from amniocentesis.[29] Individuals can make the right choice for themselves only if they have access to high-quality information about the benefits and risks of screening and if they are able to weigh that information.

Patient decision aids, which provide high-quality balanced information about difficult decisions, are instruments that help patients make the best decisions for their health care.[30] They have already been widely evaluated for treatment decisions and have been found to increase knowledge and reduce decisional conflict without increasing anxiety (see Chapter 22.2, Decision Making and the Patient). Increasingly, investigators are developing patient decision aids for screening decisions, although few have yet been evaluated.[31,32] Patient decision aids are increasingly available online.[33,34]

What Is the Effect of Uncertainty Associated With the Evidence?

There is always uncertainty about the benefits and harms of screening. The 95% *confidence interval* around the estimates of magnitude of each benefit and adverse consequence provides an indication of the amount of uncertainty in each estimate. When sample size is limited, the confidence intervals 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?

Although clinicians will be most interested in the balance of benefits and harms for individual patients, policy makers must consider issues of cost-effectiveness analysis and local resources in their decisions (see Chapter 22.1, Economic Analysis).

The USPSTF review reports that the estimated cost-effectiveness of FOBT screening is between $10 000 and $25 000 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).[1] These cost-effectiveness ratios are within the range of other screening programs such as mammographic screening for women aged 50 to 69 years (estimated at $21 400 per life-year saved),[35] ultrasonographic screening for patient with carotid stenosis (incremental cost per quality-adjusted life-year gained is estimated at $39 495),[36] and ultrasonographic screening for abdominal aortic aneurysm in men aged 60 to 80 years (estimated $41 550 per life-year gained).[37]

CLINICAL RESOLUTION

Neither the USPSTF report nor the AGA guideline provides age-specific mortality reductions attributable to screening; therefore, you cannot easily quantify the benefit for your patients in your practice unless you do it yourself, as described here. Returning to our opening clinical scenario, it is up to the patients before you to weigh whether the benefit of reduced risk of death from CRC is worth the potentially adverse consequences, including the inconvenience of colonoscopy and the complications arising from colonoscopy, the adverse effects of early

treatment for colon cancer, adverse effects of treatment, and the anxiety generated by the investigations and treatment. You may assist them to do this by providing them with a relevant patient decision aid and then reviewing their views with them. For example, if they are not bothered by the prospect of a colonoscopy, they would probably choose screening. But if they place a high value on avoiding colonoscopy now, they may prefer to reconsider screening in a few years when, because their risk for colon cancer will be higher, the balance of benefits to harms will be more favorable than it is now.

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22.4

ADVANCED TOPICS IN MOVING FROM EVIDENCE TO ACTION

GRADING RECOMMENDATIONS

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