APPLYING EVIDENCE TO THE CARE OF A HEALTHY PATIENT: HOW TO APPROACH DECISIONS ABOUT SCREENING

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Physicians are increasingly expected to know when, how, and in whom screening tests should be applied to promote the health and well-being of their patients. This article from Seminars in Medical Practice *examines how to take an evidence-based approach to deciding whether it is worthwhile to screen a patient for disease.*

You are a chief resident in internal medicine at a university-based hospital. Opening your e-mail one morning, you find a message from Susan Perry, a 52-year-old woman who has been your patient for the past 2 years. She has a question about a test for ovarian cancer she recently heard about in an e-mail forwarded by a friend.

Ms. Perry goes on to say that her friend's e-mail contained a story about a woman named Kathy. In the story, Kathy tells how she had classic symptoms of ovarian cancer but was not accurately diagnosed until her physician ordered a "CA 125" blood test, at which point she was found to have advanced-stage cancer. Kathy urges all women to insist on having this test every year as part of their annual physical exams, so they can avoid a similar outcome.

Ms. Perry says she is coming to the university's primary care clinic next week for her annual physical and wants to discuss the test with you. She closes saying, "Doctor, this e-mail really has me concerned. My aunt died of ovarian cancer after being basically healthy all her life. I don't want the same thing to happen to me if I can take steps to avoid it. Can this test help me?"

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Appropriate use of proven screening strategies is a critical patient care responsibility we have as physicians. We are increasingly expected to know when, how, and in whom preventive and diagnostic interventions should be applied to promote the health and well-being of our patients.

Recent scientific research has placed a growing emphasis on evaluating newly developed screening tests and other strategies aimed at promoting health and preventing disease. As information from these studies finds its way into the popular media, our patients will increasingly be asking us about whether they should be screened for particular diseases. To answer their questions, we need to know what the evidence says. Fortunately, we can apply the same systematic, evidence-based medicine (EBM) approach to answering questions about screening that we have used previously for questions about therapy [1] and diagnosis [2].

When applying evidence to patient care decisions, we must interpret the results from one or more studies and decide whether and how these results can help us make appropriate, cost-effective decisions on behalf of our patients. This process of translating population-based evidence into useful information to address the concerns of a specific patient is perhaps most apparent when confronting a screening question. In deciding whether it is worthwhile to screen a healthy patient, we need to consider the epidemiology of the disease in question and determine how likely *our* patient is to have that disease. We also need to know whether there is an accurate screening test that can be used and, most importantly, whether the potential benefits of using that test outweigh the potential risks of the test in a patient who is healthy.

Table 1. Principles to Guide the Screening of Healthy Populations

Burden of suffering. The disease must be a significant public health problem, leading to a burden of suffering.

Asymptomatic phase of disease. The disease must have an asymptomatic phase during which screening can be performed.

Accuracy of the screening test. A highly specific and sensitive screening test by which the disease can be diagnosed during the asymptomatic phase must be available.

Risks and benefits. Detection of the disease during the asymptomatic phase must significantly ameliorate the burden of suffering through reductions in morbidity and/or mortality. The risk of harm to those who initially test positive but do not have disease (ie, those with a false positive result) should be minimal.

This article uses the scenario of a healthy, middle-aged woman who is concerned about the mortality risks of undiagnosed ovarian cancer to examine how to apply the available evidence in deciding whether a certain screening test is worthwhile. Specifically, we will explore the principles of screening healthy populations, where to find evidence to guide screening decisions, how to appraise a research article on a screening test, and how to approach a decision about screening when the evidence is incomplete.

Assessing the Clinical Problem

You suspect that the e-mail Ms. Perry received is an "urban legend" that has been going around the Internet, and a quick search reveals several Web sites that confirm your hunch. You learn that "Kathy's Story" has been circulating since at least 1998 and was written by Carolyn Benivegna early during her treatment for primary peritoneal cancer. Furthermore, Ms. Benivegna is now advocating for women with ovarian cancer and has revised her original e-mail to state that the CA 125 test is not 100% accurate and that most doctors do not consider it to be a good screening test for ovarian cancer in healthy women [3]. You jot down the Web sites where you've found this information so you can give them to Ms. Perry. You hope that learning the original e-mail was not correct will help ease some of her concern.

Thinking about your patient's upcoming visit, you turn your attention to her specific question, "Can this test help me?" You realize you need to brush up on general principles of screening healthy patients for disease. You consult a handout from a lecture on the subject and review the main points (**Table 1**), the first of which is *burden of suffering*. In thinking about this principle, you realize your knowledge of ovarian cancer epidemiology is a bit sketchy, so you consult an electronic textbook and print a useful chapter [4] to read when you have more time.

Skimming the text later that afternoon, you learn that ovarian cancer is the seventh most common cause of cancer in women and the most common cause of death due to gynecologic malignancy [5]. The overall 5-year survival rates vary significantly with the extent of disease at the time of diagnosis, with a rate of more than 90% in women with local disease [6] and 10% in women with distant disease [7]. However, only 25% of ovarian cancers are localized at the time of diagnosis, because most women are asymptomatic in the earlier stages of the disease [8]. Although the disease carries a high mortality rate, the overall lifetime risk of developing ovarian cancer is only 1.4% to 1.8% in U.S. women [9]. The lifetime risk is higher in women with certain risk factors. A first- or second-degree relative with ovarian cancer, for example, would increase the lifetime risk to 3.7% [10].

Based on your background reading, ovarian cancer meets the burden of suffering. There is also an asymptomatic phase in which screening could be performed, and the treatment for ovarian cancer is clearly more effective if started when the cancer is at an early stage. Theoretically, you surmise, a successful screening test for asymptomatic women could lead to thousands of lives saved per year.

Pulling up Ms. Perry's electronic medical record, you see that she underwent menopause at age 49, started menstruating at age 15, and has had three children. Her past medical history is notable only for gastroesophageal reflux and hyperlipidemia. While her family history is positive for a paternal aunt who died of ovarian cancer, this is her only risk factor for the disease. Based on her history and the information in your textbook, you feel Ms. Perry's lifetime risk for developing ovarian cancer is approximately 3.7%. Although this risk is still fairly low, you recall that Ms. Perry is interested in doing what she can to prevent disease. She has been quite conscientious about getting regular cancer screenings, including yearly mammograms and Pap smears and a colonoscopy 2 years ago.

The first step in the EBM process—assessment—involves the following components: 1) gathering accurate, patient-specific data pertinent to the

problem or patient care concern and assessing the patient's perspective on the issue; 2) determining the urgency, timing, and magnitude of the concern (for the patient as well as the relevant population); and 3) assessing the state of the evidence as well as your own knowledge on the subject. In this case, the central concern is our patient's desire to take steps to avoid death from ovarian cancer. Thus, an important goal of our assessment is to gather information that helps us approach the question of whether screening is worthwhile for Ms. Perry. Several principles of screening healthy populations are useful to consider here (Table 1), including the *burden of suffering* caused by ovarian cancer and whether the disease has an *asymptomatic phase* during which screening can be performed.

Burden of Suffering

The burden of suffering reflects not only the morbidity and mortality caused by the disease in question but also the frequency within the population and the likelihood that the disease will progress beyond the asymptomatic phase. Consider, for example, hypertension. Given the high prevalence of this disease in the general population, its long asymptomatic phase, and its association with an increased incidence of life-threatening conditions (ie, stroke, coronary artery disease, and congestive heart failure), few would argue that identifying those individuals with hypertension is not efficacious.

The evidence-based approach to Ms. Perry's case, thus, begins with assessing the burden of suffering caused by ovarian cancer. At the population level, this means considering the epidemiology of ovarian cancer. Being unsure of the incidence and natural history of ovarian cancer and the risk factors for the disease, you have appropriately consulted a current medical textbook to obtain this background information. After reviewing the screening handout, reading about the epidemiology of ovarian cancer, and checking your patient's chart, you have made the following conclusions: 1) ovarian cancer carries a significant burden of suffering but is relatively uncommon, 2) your patient's concern about developing ovarian cancer is quite high, but her baseline risk for the disease is relatively low, and 3) screening an asymptomatic woman like your patient would appear to be worthwhile *if* a successful screening test were available. Yet to be assessed are the state of the evidence on screening for ovarian cancer and your own understanding of the value of CA 125 testing for your patient.

Several days pass and it is the evening before Ms. Perry's visit. Checking the clinic schedule, you see that she will be coming in at 10 AM tomorrow. You recall her e-mail and realize you are not ready to address her question. Based on your reading so far, you have determined that screening is theoretically worthwhile. However, you are not familiar with how the CA 125 test performs as a screening tool and realize you need this information before you can fully explore whether the test is of value for screening a patient like Ms. Perry. Once again you consult your electronic textbook, which offers a useful discussion of the test's performance [11].

You learn that CA 125 is a tumor marker that is shed into the bloodstream by malignant cells derived from müllerian ducts and cells lining the peritoneum, pleura, and pericardium [12]. The average reported sensitivity of the CA 125 test for detecting stage I disease is 50% [10]. Levels of CA 125 are increased in patients with ovarian cancer but also in patients with other malignancies or with certain benign conditions and in a small number of healthy women, indicating limited specificity of the test.

The text goes on to review the results of several screening studies that have been performed in postmenopausal women. Based on these, the estimated sensitivity of the CA 125 test for detecting preclinical disease is 70% to 80%, the specificity of a single test is 98.6% to 99.4%, and the positive predictive value of an annual CA 125 test is 3% in women of average risk and 10% in women with one first- or second-degree relative with a history of ovarian cancer [10]. The authors add that specificity may be enhanced by combining the CA 125 test with transvaginal ultrasonography, by measuring levels serially, or by raising the reference level of CA 125 that constitutes a positive test. Finally, the text indicates that CA 125 screening for ovarian cancer is being studied in three randomized controlled trials (RCTs) that are currently underway.

Before we can decide whether to recommend the CA 125 test to Ms. Perry, we need to consider the *accuracy of the test* for detecting ovarian cancer in asymptomatic women and the implications of the possible test results.

Accuracy of the Screening Test

Figure 1 shows the possible results of a screening test. The number of people who fall into each group depends on the sensitivity and specificity of the test. Knowing the high mortality risks associated with ovarian cancer, we

	DISEASE STATE		
	Present	**Absent**	
Positive	**True positive** These people will benefit from the test, as they have disease that will be revealed.	**False positive** These people will require additional tests and procedures to prove that they do not have disease.	**Positive predictive value** = the percentage of those who test positive who actually have disease
Negative	**False negative** These people will be falsely reassured that they do not have disease when, in fact, they do have disease.	**True negative** These people will appropriately be found to not have disease but may have had anxiety about undergoing the test.	**Negative predictive value** = the percentage of those who test negative who actually are free of disease
	Sensitivity = the percentage of those with disease who test positive	**Specificity** = the percentage of those without disease who test negative	

(Left axis label: TEST RESULT)

Figure 1. Potential results of a screening test and their implications.

can see that a *true positive* or a *true negative* result would be beneficial to our patient. That is, revealing the presence of cancer at an early, asymptomatic stage would give our patient the best chance of prolonged survival, whereas revealing the absence of cancer would be highly reassuring. However, even in these cases, it is worth remembering that a patient can experience psychological stress simply by having a test done and needing to wait for the results. On the other hand, a *false negative* or a *false positive* result would have the potential to cause real harm to our patient; the former would lead to the false reassurance about the absence of disease, whereas the latter would lead to our patient undergoing unnecessary tests or treatments and, thus, risking complications or side effects as well as costs and inconvenience.

When deciding whether a screening test has adequate sensitivity and specificity for the disease in question, we must first consider the prevalence of the disease within the population being screened. For a condition that is relatively rare, such as ovarian cancer, there will be many more false positive than true positive results, leading to further, potentially invasive evaluations in otherwise healthy individuals. The *positive predictive value*, or the likelihood that a positive test result represents true disease, will vary depending on the prevalence of disease in the population being screened. For example, according to the research findings summarized in **Table 2**, the positive predictive value of the CA 125 test is only 3% in women at average risk for ovarian cancer but increases to 10% for women with one relative with ovarian cancer [10].

This means that, among women at average risk, for every patient with a true positive result there will be 30 other patients who will have a false positive result. Even at Ms. Perry's slightly higher risk level (ie, with a family history of ovarian cancer in one relative), the data suggest that for every patient who is identified correctly as having disease there will be at least 9 other patients who need additional testing, perhaps even surgery, to prove that their test result was false positive.

Asking a Focused Clinical Question

After reviewing the background information on the CA 125 test, you have reason to doubt the test's value for screening Ms. Perry. Recognizing the evolving state of the evidence and your patient's potentially important family history, you want to know whether more recent information is available that can help you more conclusively determine the value of CA 125 testing in Ms. Perry's case. You reason that a recently published national guideline might provide this information and would be the most efficient way to get an answer. But, you also are curious whether any of the RCTs mentioned in your textbook has been completed and reported in the literature. You frame an explicit clinical question to help guide your search for original research evidence.

Having background knowledge is useful for developing a focused clinical question. While background questions can be answered using a well-referenced

Table 2. Positive Predictive Value (PPV) of CA 125 Screening for Ovarian Cancer

	PPV, average risk*	PPV, higher risk†	Sensitivity	Specificity
Serum CA 125 alone	3%	10%	80%	99%
Serum CA 125 plus ultrasonography‡	12%–28%	29%–55%	80%	99.7%–99.9%

Adapted from Carlson et al [10].

*No family history of ovarian cancer.

†One relative with ovarian cancer.

‡Transvaginal ultrasonography performed if abnormal CA 125 test result.

textbook, foreground questions often require an active search of the primary research literature, and a clearly stated question allows us to search more efficiently for current evidence that will be helpful. The PICO framework (patient, intervention, comparison, outcome) is a useful approach for developing a focused clinical question [13]. The PICO components in this case might be defined as:

P = healthy, asymptomatic postmenopausal woman

I = serum CA 125 test for ovarian cancer

C = no test

O = prolonged survival

Using this framework to build a focused clinical question, our question in Ms. Perry's case would be:

> In a **healthy, asymptomatic, postmenopausal woman**, does **screening with a CA 125 test** for ovarian cancer lead to **prolonged survival**, compared with **no testing**?

Acquiring the Current Best Evidence

You start your search for evidence at the National Guidelines Clearinghouse (www.guideline.gov). A search for "ovarian cancer" reveals 18 matches, only one of which addresses screening for ovarian cancer. This guideline, released in 2002 by the Institute for Clinical Systems Improvement, recommends against using a CA 125 test to screen asymptomatic women [14]. You print a copy of this guideline. You then check the American Cancer Society (ACS) Web site (www.cancer.org), where cancer information links lead you to a patient-oriented summary statement that the CA 125 test is not recommended for ovarian cancer screening of women without known strong risk factors [15]. You also print this summary.

#	Search History	Results
1	Exp *Ovarian Neoplasms/pc, di [Prevention & Control, Diagnosis]	2697
2	Limit 1 to (human and English language and clinical trial)	46

Figure 2. The search history from OVID: MEDLINE Database 1966 to October Week 5 2002. The *explode* (exp) function allows you to include more specific and relevant terms in your search strategy by automatically including the broad term and all related terms indented under it (eg, exploding "ovarian neoplasms" would include specific subtypes of this type of cancer). The *focus* (*) function indicates that you want ovarian neoplasms to be the main subject of the article, an efficient way to limit your search to the most relevant articles. The addition of the subheadings (/pc, di) further limits the search to articles that would be likely to address screening and diagnosis.

Feeling increasingly confident that the test is not worthwhile for Ms. Perry, you try one more site—the National Cancer Institute (NCI; www.nci.nih.gov), where you find a recent evidence-based summary of ovarian cancer screening [16]. The summary provides a concise and reasoned review of the available evidence to date, which it states does not support the use of CA 125 alone for routine screening for ovarian cancer. You print this summary as well.

You then turn to MEDLINE to see whether any of the RCTs involving CA 125 have been reported in the literature. You search using the MeSH (Medical Subject Heading) term "ovarian neoplasms," limiting this term to the subheadings "diagnosis" and "prevention and control." To focus on articles addressing therapy, you additionally limit your search to "clinical trial" as the publication type. Your search yields 46 articles (**Figure 2**). Scanning the titles, you find that the most recent RCT, entitled, "Screening

Table 3. Internet Resources for Locating Evidence About Screening Tests

Resource	Comments
National Guidelines Clearinghouse (www.guideline.gov)	This Web site is maintained by the Agency for Healthcare Research and Quality and offers a searchable database of evidence-based clinical practice guidelines from a wide range of national organizations.
Health Services Technology Assessment Texts (hstat.nlm.nih.gov)	This Web site is maintained by the National Library of Medicine and offers a searchable database of full-text guidelines, technology assessments, and health information to support clinical decision making. It also allows users to search external databases (ie, National Guidelines Clearinghouse, PubMed, and Centers for Disease Control and Prevention guidelines).
Relevant professional organizations	A general Internet search for relevant medical specialty associations or societies, public or private organizations, or government agencies may be worthwhile for locating specific clinical recommendations. Web sites will vary in their completeness and ease of use.
MEDLINE/PubMed (www.ncbi.nlm.nih.gov/Pubmed)	This Web site is maintained by the National Library of Medicine and consists of a searchable bibliographic database of references and abstracts from more than 4500 biomedical journals. Limiting MEDLINE searches to evidence-based reviews can save time.

for ovarian cancer: a pilot randomised controlled trial," was published in the *Lancet* in 1999 [17]. You recognize this study from the references cited in your textbook chapter, so you surmise that no more recent RCT is available. You decide to print this study so you can scrutinize it for information that will help you in your discussion with Ms. Perry.

Having spent roughly 30 minutes on these searches, you are now armed with a set of clinical guidelines, summaries from the ACS and NCI, and a pilot RCT. You take this information home with you to review in more depth tonight.

There are many reliable resources for locating evidence about screening tests (**Table 3**). Although the primary medical literature would be the most comprehensive resource, a MEDLINE search may not be the most efficient first step. In addition, it can be difficult to place one or two articles about a screening test in the context of the overall literature.

For these reasons, it may be most efficient to start by looking for a summary of the literature, and a good place to begin is with a search for recent clinical practice guidelines. The National Guidelines Clearinghouse has hundreds of guidelines but is not exhaustive. In our case, we were able to find more useful summaries of the literature by consulting Web sites for relevant professional organizations. Guidelines can also be a good source for obtaining answers to background questions and can point you to the primary sources used in the literature review. However, they remain a mix of evidence and opinion.

If you are interested in reviewing the primary literature or you want to be sure that you have the most current evidence, performing a MEDLINE search is the best option. The most efficient means to locate articles that address screening depends on which aspect of screening you are most interested in. For example, information about the accuracy of the test under consideration would be best found using a search strategy for diagnosis articles, whereas evidence pertaining to the benefit of early diagnosis and treatment would be best located using a search strategy for therapy articles. Because our question deals with whether screening for ovarian cancer results in prolonged survival, a therapy article may be most useful. Limiting our search to clinical trials is an effective way to find this type of article.

Appraising Evidence for Validity and Importance

After dinner, you skim the guidelines and expert summaries. After 15 minutes you are confident that no important national organization currently recommends using CA 125 as a screening test for ovarian cancer in asymptomatic postmenopausal women at average risk for the disease.

You now turn to the RCT and examine it more closely using criteria for appraisal of an article on screening (**Table 4**). The study involved 22,000 women who were randomized to either screening with CA 125 followed by pelvic ultrasonography if the CA 125 test result was abnormal or to no screening [17]. The patients were followed for 7 years; both survival and

overall ovarian cancer mortality between the two groups were compared. As expected, survival from the time of diagnosis of ovarian cancer was longer in the screened group, which you realize might reflect *lead-time bias*. Overall ovarian cancer mortality, however, did not differ significantly.

Screening detected an index cancer in six patients, and 23 of the screened patients had false positive screening results. The positive predictive value of an abnormal screening result was 20.7%, meaning that almost 80% of the patients having abnormal screening tests did not have ovarian cancer (but did need to undergo surgical investigation to exclude malignancy). During the 7-year follow-up, 10 additional cancers were identified in the screened group and 20 were found in the control group. Median ovarian cancer survival in the screened group was 73 months versus 42 months in the control group. There were twice as many deaths due to ovarian cancer in the control group compared with the screened group, although this was not statistically significant. Because the women with ovarian cancer in the control group had an unexpectedly poor outcome, the benefits from screening on survival and mortality might be misleading. The authors also were careful to note that this was a feasibility study; it was not designed (and therefore did not have the power) to detect moderate changes in mortality. Finally, the psychosocial implications of false positive screening results and the cost-effectiveness of this screening program were not addressed in the study.

This study is important in that it was one of the first to demonstrate the feasibility of mass screening for ovarian cancer using the CA 125 test. It is prospective and randomized, both features that make this a well-designed study. However, as the authors note, the study was not designed to be able to show moderate survival benefits that could be achieved using the screening strategies under investigation, although it does set the stage for larger trials that may show such benefits. While this is not the perfect study to answer our question, it is the best that we have at this time. Conveying the incomplete state of the evidence to our patient will be important.

The issue of *lead-time bias* is an important consideration in studies of screening. Lead-time bias refers to the fact that screening can lead to a disease being found at an earlier stage than it might otherwise have been diagnosed. Thus, it may then appear that those who were screened live longer, when in reality they were simply diagnosed earlier.

Table 4. Criteria for Appraising and Applying the Results of an Individual Screening Study

Are the recommendations valid?

Is there randomized trial evidence that earlier intervention works?

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 risks and benefits?

How do the risks and benefits compare in different people with different screening strategies?

What is the impact of individuals' values and preferences?

What is the impact of uncertainty associated with the evidence?

What is the cost-effectiveness?

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Applying Evidence to Patient Care

The next day, you see Ms. Perry in the waiting room. You are glad you have information to share with her, and you hope that she will accept the uncertain nature of the available evidence. As you enter the exam room, Ms. Perry appears anxious, so you decide to address her question immediately.

"Hi, Ms. Perry. I want to begin by telling you that I looked into Kathy's Story. It's a story that has been circulating the Internet for years, and it's not totally accurate. But you did raise a good question, and I want to be sure to address your concerns as best as I can."

You go on to describe how the CA 125 test alone is not very accurate in detecting early-stage ovarian cancers, especially in women without extensive risk factors for ovarian cancer, like Ms. Perry. You discuss the risks associated with screening, particularly the potential for exposure to further, possibly invasive studies in the event of a false positive test result. You also mention that even with the use of ultrasonography, CA 125 screening has not been clearly demonstrated to save lives. You conclude saying, "For these reasons, Ms. Perry, I would not recommend that you have the CA 125 test. Do you agree?"

Ms. Perry, who has listened closely to your explanation, says that she does agree with your recommendation. She expresses her thanks for your interest in taking the time to explain what you have learned about the CA 125 test.

You then move on to address the original reason

Table 5. Summary of the Evidence-Based Medicine Approach to Deciding Whether to Screen Ms. Perry for Ovarian Cancer

Assess	
The patient	Ms. Perry is an asymptomatic, postmenopausal woman who has been generally healthy. She receives an e-mail that raises her concern about needing annual CA 125 testing to screen for ovarian cancer. You estimate that her lifetime risk for ovarian cancer is approximately 3.7%.
The problem	Does CA 125 screening for ovarian cancer in patients like Ms. Perry make a difference in terms of long-term outcomes?
Ask	In a healthy, asymptomatic postmenopausal woman, does screening with a CA 125 test for ovarian cancer lead to prolonged survival, compared with no testing?
Acquire	One guideline from the National Guidelines Clearinghouse and two evidence-based summaries, one from the ACS and one from the NCI (< 20 minutes to obtain)
	Full text of a pilot randomized controlled trial (RCT) from MEDLINE (< 15 minutes to obtain)
Appraise	The guideline and evidence-based summaries state that there is no reliable evidence to advocate use of CA 125 test in screening women at average risk for ovarian cancer. (~ 10 minutes to read)
	The pilot RCT was randomized and prospective but was not designed to detect moderate changes in mortality and did not consider the impact of patient values and preferences or cost-effectiveness. However, the study did suggest that a combined approach to screening (ie, with CA 125 plus trans-vaginal ultrasonography) may prolong survival but does not reduce mortality. (~ 30 minutes to read and evaluate)
Apply	Screening asymptomatic women for ovarian cancer with the CA 125 test alone is not beneficial. In addition, the low positive predictive value for this test means that many women without cancer would have to undergo invasive procedures in order to find the one woman who has cancer. Over time, the evidence may support screening, but for now you decide not to screen Ms. Perry.

ACS = American Cancer Society; NCI = National Cancer Institute.

for Ms. Perry's visit, which is an annual physical exam. At the close of the visit you return to the topic of ovarian cancer screening.

"Before you leave Ms. Perry, are you sure you have no further questions about the CA 125 test?"

"No, I'm pretty comfortable with what you told me. I do wish, however, that there was a reliable test for ovarian cancer."

You then tell her about three large-scale ovarian cancer screening trials that are ongoing, using either transvaginal ultrasonography alone as a screening test or a combination of CA 125 and ultrasonography. You conclude saying, "Almost 400,000 women are expected to be enrolled in the trials, so we hope to have more evidence soon on which to base our recommendations."

Risks and Benefits

When applying evidence about a screening test to the care of a patient, we need to consider the consequences to our patient of performing the test. One of the most important considerations is whether the potential risks outweigh the potential benefits.

Potential risks in this case include financial costs associated with the test itself, physician visits, and possible surgeries, including the unnecessary surgeries that could result from a false positive result. Potential psychological risks include the increased anxiety from having the test, the false reassurance of a false negative test result, and the avoidable stress of a false positive test result. The most concerning risk of a false positive test, however, would be the potential harm to Ms. Perry of an exploratory laparotomy required to prove that she does not have disease. How many such surgeries would we be willing to tolerate for each diagnosis of cancer at an asymptomatic stage? As physicians, we abide by the Hippocratic Oath, which cautions us to "First, do no harm." Inducing harm through our screening actions runs counter to our principles. An important difference between weighing the potential benefits and harms of preventive (screening) interventions and assessing the costs and benefits of therapeutic interventions is that we will not accept the same level of risk in a patient who is

healthy *before* the intervention is applied.

Patient Values and Preferences

A second critical consideration in deciding whether screening is worthwhile is to assess the importance of our patient's values and preferences. While the research study we evaluated did not consider these points, patient values and preferences are at the heart of applying population-based evidence to individual patients. Guidelines and recommendations about screening are essentially made for populations of patients. It is our job to clearly communicate the available evidence to our patient and to take into account her wishes. Ms. Perry may still have desired to have the CA 125 test performed, even after we carefully explained the lack of evidence for using the test to screen for ovarian cancer and the potential impact of a false negative or false positive result. On the other hand, if this test were to be recommended in the future, some patients might choose not to have the test done. In every case, we must take time to understand our patient's point of view. In this case, Ms. Perry's concern about the e-mail was addressed at the outset of her visit, significantly alleviating her anxiety.

Uncertainty of the Evidence

Finally, there is often uncertainty associated with the evidence, and this case is no exception. While the current recommendations do not support screening women at average risk for ovarian cancer, additional studies are ongoing. By effectively communicating the uncertainty of the currently available evidence while informing Ms. Perry that additional, perhaps more conclusive, information may be forthcoming, we have done all that we can to ensure that our patient is well informed about a subject that is important to her.

Conclusion

Table 5 summarizes the five-step EBM approach as it applies to the decision whether to screen Ms. Perry for ovarian cancer using the CA 125 test. Well more than an hour was spent searching for, evaluating, and assimilating the background knowledge and available evidence used to address the central question in this case. Given limited time for researching clinical questions that arise in our daily practice, it is clear that we need easily accessible, concise, and specific information. Furthermore, we need assurance that the information source we choose is reliable, cognizant of recent and ongoing research, and representative of the majority of viewpoints on the topic in question.

In some cases, an up-to-date, systematically developed clinical practice guideline may provide the specific information we need to address our question. Although it is not feasible to be knowledgeable about all recently published or updated guidelines, knowing when and where to search for relevant guidelines can help us be more efficient in seeking answers to our clinical questions.

Finally, as this case illustrates, a critically important EBM skill is the ability to communicate population-based evidence in a manner that recognizes the potential fears, concerns, or anxiety of our patients and that appreciates the evolving state of the available medical information. Effectively explaining the evidence to our patients in a way that they can understand and then integrating their values and preferences into our decision making is the true art of medicine.

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