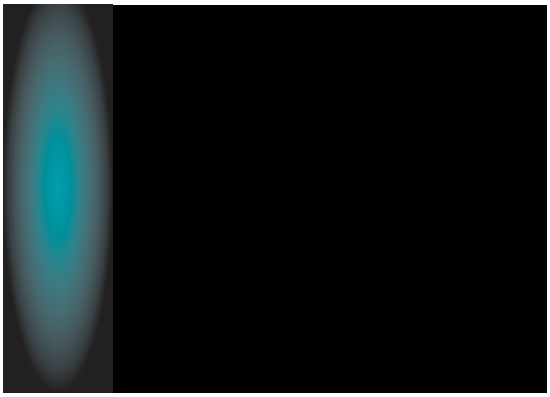
Principles and Practice of Secondary Prevention



CHAPTER OUTLINE

Secondary prevention is based on early detection of disease, through either screening or case finding, followed by treatment. **Screening** is the process of evaluating a group of people for asymptomatic disease or a risk factor for developing a disease or becoming injured. In contrast to case finding (defined later), screening usually occurs in a **community setting** and is applied to a population, such as residents of a county, students in a school, or workers in an industry. Because a positive screening test result usually is not diagnostic of a disease, it must be followed by a *diagnostic* test. For example, a positive finding on a screening mammogram examination must be followed by additional diagnostic imaging or a biopsy to rule out breast cancer.

As shown in Figure 16-1, the process of screening is complex and involves a cascade of actions that should follow if each step yields positive results. In this regard, initiating a screening program is similar to boarding a roller coaster; participants must continue until the end of the process is reached. Many members of the public assume that any screening program will automatically be valuable or cost-effective; this explains the popularity of mobile imaging vans that offer full-body computed tomography (CT) and the direct-to-consumer marketing of genomic analysis. In contrast, many preventive medicine specialists demand the same standards of evidence and cost-effectiveness as for therapeutic interventions in patients with known disease. A case may be made for even higher standards. Screening means looking for trouble. It involves, by definition, people with no perception of disease, most of whom are well; therefore great potential exists to do net harm if screening is performed haphazardly.

Screening usually is distinguished from **case finding,** which is the process of searching for asymptomatic diseases and risk factors among people in a **clinical setting** (i.e., among people who are under medical care). If a patient is being seen for the first time in a medical care setting, clinicians and other health care workers usually take a thorough medical history and perform a careful physical examination and, if indicated, obtain laboratory tests. Establishing baseline findings and laboratory values in this way may produce case finding, if problems are discovered, and is considered "good medicine" but is not referred to as "screening."

A program to take annual blood pressure of employees of a business or industry would be considered screening, whereas performing chest radiography for a patient who was just admitted to a hospital for elective surgery would be called "case finding." The distinction between screening and case finding is frequently ignored in the literature and in practice. Most professional societies do not distinguish between the two in their recommendations regarding screening. We use the two terms interchangeably in this chapter. Chapter 7 discusses some of the quantitative issues involved in assessing the accuracy and performance of screening, including sensitivity, specificity, and predictive value of tests. In this chapter we assume the reader is comfortable with these concepts. The purpose here is to discuss broader public health issues concerning screening and case finding. Chapter 18 provides an extensive discussion of the U.S. Preventive Services Task Force in the clinical encounter.

I. COMMUNITY SCREENING

A. Objectives of Screening

Community screening programs seek to test large numbers of individuals for one or more diseases or risk factors in a community setting (e.g., educational, work, recreational) on a voluntary basis, often with little or no direct financial outlay by the individuals being screened (Table 16-1).

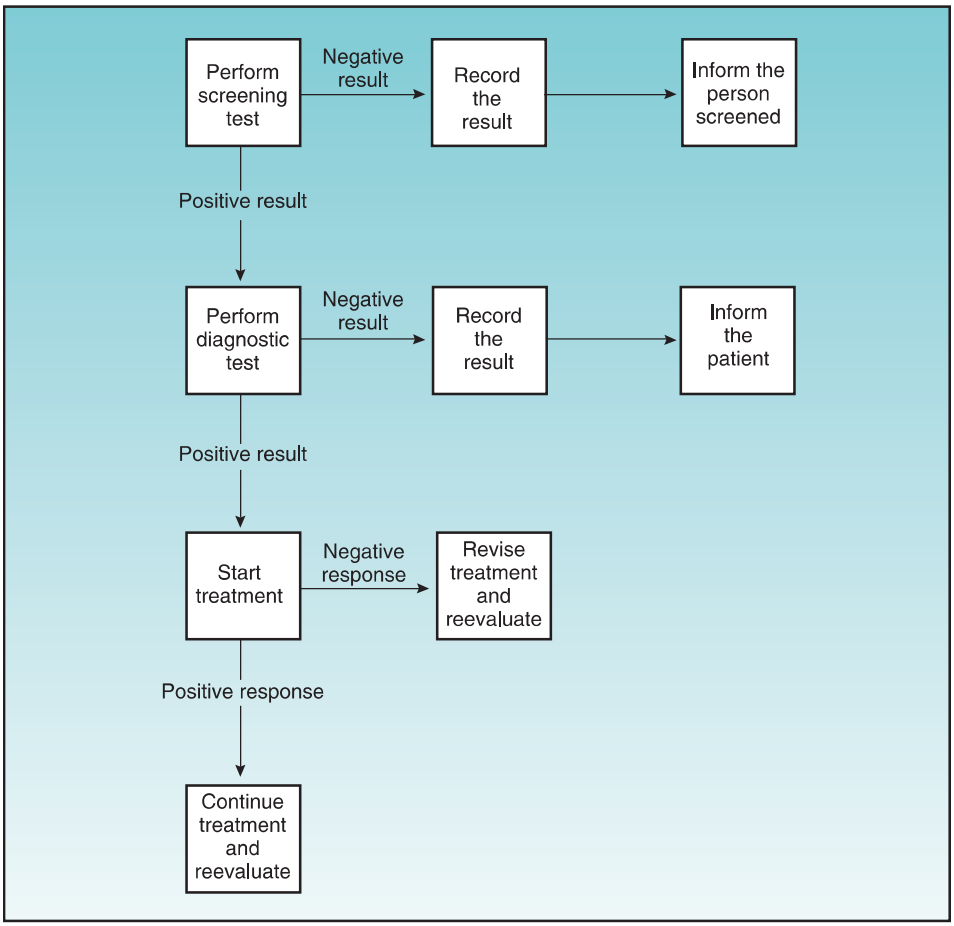


Figure 16-1 The process of screening.

Table 16-1 Objectives of Screening Programs

Target	Objective	Examples
Disease		
	Treatment to reduce mortality	Cancer
	Treatment to prevent complications	Hypertension
	Treatment to eradicate infection and prevent its spread	Gonorrhea, syphilis, tuberculosis
	Change in diet and lifestyle	Coronary artery disease, type 2 diabetes mellitus
Risk Factors		
Behavioral	Change in lifestyle	Cigarette smoking, unsafe sexual practices
Environmental	Change in occupation	Chronic obstructive pulmonary disease from work in a dusty trade
Metabolic	Treatment or change in diet and lifestyle	Elevated serum cholesterol levels

B. Minimum Requirements for Community Screening Programs

The minimum requirements for establishing a safe, ethical, and cost-effective screening program fall into the following three areas:

- Disease requirements
- Screening test requirements
- Health care system requirements

If any of the requirements is not at least partially met, an extensive population-wide screening program may be inappropriate. Table 16-2 outlines these requirements in four common screening programs, for hypertension, high cholesterol, cervical cancer, and ovarian cancer, as further discussed in Application of Minimum Screening Requirements to Specific Programs.

1. Disease Requirements

1. The disease must be *serious* (i.e., produce significant morbidity or mortality), or there is no reason to screen in the first place.
2. Even if a disease is serious, there must be an *effective therapy* for the disease if it is detected. Screening is of no value unless there is a good chance that detecting the

Table 16-2 Requirements for Screening Programs and Ratings of Example Methods to Detect Hypertension, Elevated Cholesterol Levels, Cervical Cancer, and Ovarian Cancer

Requirements	Screening Method and Rating*			
	Sphygmomanometer Reading (Hypertension)	Serum Cholesterol Test (Dyslipidemia)	Pap Smear (Cervical Cancer)	Computed Tomography (Ovarian Cancer)
Disease Requirements				
Disease is serious.	++	++	++	++
Effective treatment exists.	++	+	+	+/–
Natural history of disease is understood.	++	+	++	+
Disease occurs frequently.	++	++	++	++
Other diseases or conditions may be detected.	–	–	–	+
Screening Test Requirements				
Test is quick to perform.	++	+	+	++
Test is easy to administer.	++	+	+	+
Test is inexpensive.	++	+	+	+
Test is safe.	++	++	+	+
Test is acceptable to participants.	++	+	+	++
Sensitivity, specificity, and other operating characteristics are acceptable.	++	+	+	–
Health Care System Requirements				
Method meets the requirements for screening in a community setting.	++	++	+	–
Method meets the requirements for case finding in a medical care setting.	++	++	++	+

*Ratings are applied to four conditions for which community screening has often been undertaken: hypertension, tested by a sphygmomanometer reading of blood pressure; elevated cholesterol levels, with total cholesterol measurement based on a rapid screening of blood; cervical cancer, tested by Papanicolaou (Pap) smear; and ovarian cancer, tested by computed tomography (CT) scanning. Ratings are as follows: ++, good; +, satisfactory; –, unsatisfactory; +/–, depends on disease stage.

disease in the *presymptomatic stage* would be followed by effective therapy. Furthermore, the benefits of detecting the condition in a few people should outweigh the harms that occur (and accrue) to people with a false-positive test, including unnecessary, invasive workups and treatment. For example, at present, there is no value in screening for pancreatic cancer because the chance of cure by standard medical and surgical methods is extremely small. The controversy around prostate cancer screening is largely about the benefits of treatment versus the possible harm of unnecessary treatment.

3. The natural history of a disease must be understood clearly enough to know that there is a significant window of time during which the disease is detectable, and a cure or at least effective treatment would occur. For example, colon cancer follows an established disease mechanism from small polyps in the colon to colon cancer. Early detection and surgical removal of a polyp in the colon could prevent intestinal obstruction and morbidity, and likely is curative.
4. The disease or condition must not be too rare or too common. Screening for a rare disease usually means that many false-positive test results would be expected for each true finding (see Chapter 7). This increases the cost and difficulties of discovering persons who truly are ill or at high risk, and it causes anxiety and inconvenience for individuals who must undergo more testing because of false-positive results. Unless the benefits from discovering one case are very high, as in treating a newborn who has phenylketonuria or congenital hypothyroidism, it is seldom cost-effective to screen general populations for a rare disease.

Screening for common conditions may produce such a large proportion of positive results that it would not be cost-effective; common conditions are best sought in the context of care. It is possible, however, that screening for some common risk factors, such as elevated cholesterol levels, may provide opportunities for education and motivation to seek care and behavior change.

2. Screening Test Requirements

1. The screening test must be reasonably quick, easy, and inexpensive, or the costs of large-scale screening in terms of time, effort, and money would be prohibitive.
2. The screening test must be safe and acceptable to the persons being screened and to their clinicians. If the individuals to be screened object to a procedure (as frequently occurs with colonoscopy), they are unlikely to participate.
3. The sensitivity, specificity, positive predictive value, and other operating characteristics of a screening test must be known and acceptable. False-positive and false-negative test results must be considered. An additional difficulty in using screening tests in the general population is that the characteristics of the screening test may be different in the population screened from the population for whom the screening was developed.

3. Health Care System Requirements

1. People with positive test results must have access to follow-up. Because screening only sets apart a high-risk group, persons who have positive results must receive

further diagnostic testing to rule in or rule out actual disease. Follow-up testing may be expensive, time-consuming, or painful, with some risk. With many screening programs, most of the efforts and costs are in the follow-up phase, not in the initial screening.

2. Before a screening program for a particular disease is undertaken, treatment already should be available for people known to have that disease. If there are limited resources, it is not ethical or cost-effective to allow persons with symptoms of the disease to go untreated and yet screen for the same disease in apparently well persons.
3. Individuals who are screened and diagnosed as having the disease in question must have access to treatment, or the process is ethically flawed. In addition to being unethical, it makes no medical sense to bring the persons screened to the point of informing them of a positive test result and then abandon them. This is a major problem for community screening efforts because many people who come for screening have little or no medical care coverage. Therefore, the cost for the evaluation of the positive screening tests and the subsequent treatment (if disease is detected) are often borne by a local hospital or other institution.
4. The treatment should be acceptable to the people being screened. Otherwise, individuals who require treatment would not undertake it, and the screening would have accomplished nothing. For example, some men may not want treatment for prostate cancer because of possible incontinence and impotence.
5. The population to be screened should be clearly defined so that the resulting data are epidemiologically useful. Although screening at "health fairs" and in shopping centers provides the opportunity to educate the public about health topics, the data obtained are seldom useful because the population screened is not well defined and tends to be self-selected and highly biased in favor of those concerned about their health.[1]
6. It should be clear who is responsible for the screening, which cutoff points are to be used for considering a test result "positive," and how the findings will become part of participants' medical record at their usual place of care.

4. Application of Minimum Screening Requirements to Specific Programs

Table 16-2 applies the previously described criteria to the following four conditions for which community screening has been undertaken:

- Hypertension, tested by a sphygmomanometer reading of blood pressure
- Elevated cholesterol levels, based on a screening of blood
- Cervical cancer, with Papanicolaou smear
- Ovarian cancer, for which CT scan screening was considered but rejected

As shown in Table 16-2, screening for hypertension, hypercholesterolemia, and cervical cancer generally fulfill the minimum requirements for a community screening program. Investigators have agreed that a screening program using CT scans to detect ovarian cancer in the general population fails at two critical points. First, the yield of detection is low. Second, as numerous studies have shown, only a small proportion of cancers can be cured by the time they are detected.[2] Because of these problems, community screening for ovarian cancer is not recommended.

For many screening programs, debate surrounds general screening issues such as what age to start the screening, when to stop, how often to repeat the screening, and whether the methods yield accurate results. Screening for breast cancer is an example of a controversial screening program because the benefits seem to be less than originally hoped and risks are associated with screening mammography.[3] The age at which to begin screening women for breast cancer is particularly controversial because breast cancer is less common in younger women, but often more aggressive than later in life, and the risks of screening (e.g., false positives) are higher (Box 16-1).

C. Ethical Concerns about Community Screening

The ethical standards are important to consider when an apparently well population of individuals who have *not* sought medical care is screened. In this case the professionals involved have an important obligation to show that the benefits of being screened outweigh the costs and potential risks. The methods used in performing any public screening program should be safe, with minimal side effects.

D. Potential Benefits and Harms of Screening Programs

The potential benefits of screening include reduced mortality, reduced morbidity, and reassurance. With the goal of screening programs to identify disease in the early, presymptomatic stage so that treatment can be initiated, the potential benefits are reduced mortality for many programs. However, some screening programs have a goal of early detection using less invasive treatment (e.g., taking a small piece of breast tissue rather than removing the entire breast). Another potential benefit of screening is the reassurance to both individuals and providers.

The potential adverse effects (harms) of all screening programs need to be considered. Some screening procedures may be uncomfortable, such as mammography, or require preparation, such as colonoscopy (colon cleansing). Colonoscopy also carries procedural risks (bleeding, perforation). Other harms of screening include anxiety from false-positive results, false reassurance for patients with false-negative tests, and costs to individuals and society from lost work.

Test errors are a major concern in screening (see Chapter 7). **False-positive test results** lead to extra time and costs and can cause anxiety and discomfort to individuals whose results were in error. In the case of screening for breast cancer, one study showed that the more screening mammograms or clinical breast examinations given, the more likely one or more false-positive results occurred.[4] An estimated 49% of women who had undergone 10 mammograms had at least one false-positive reading, equal to a false-positive error rate of 6% to 7% on each mammogram.

False-negative test results can be even worse. One implied promise made to people is that if they are screened for a particular disease and found to have negative results, they need not worry about that disease. False-negative results may lead people with early symptoms to be less concerned.

Box 16-1 Screening Controversies: "Are you really saving lives? And how much worry and lost quality of life is one life saved worth?"

Breast cancer and prostate cancer in particular illustrate the challenge in weighing evidence of small changes in mortality against side effects of screening and treatment. Because of the impact of screening biases, only a change in overall mortality in the screened population is considered evidence of an effective screening program. The debate about changes in the U.S. Preventive Services Task Force (USPSTF) recommendations on breast cancer also demonstrate that few issues in preventive medicine have more power to polarize the public, politicians, and health care professionals than screening.[30]

Breast Cancer

Many women die prematurely of breast cancer. Unfortunately, only a fraction of breast abnormalities detected on a mammogram truly lead to a saved life; the majority are false-positive findings or lead to unnecessary diagnosis and treatment of lesions such as ductal carcinoma in situ (DCIS), which is not harmful to the majority of women. Most women would not have known they had these DCIS lesions had it not been for the screening mammography. Women with DCIS are at increased risk for a subsequent diagnosis of invasive breast cancer. Unfortunately, we cannot predict which women with DCIS will ultimately go on to have invasive breast cancer. Thus, women who are diagnosed with DCIS after a screening mammography often undergo breast surgery, chemotherapy, and radiation treatment that can be costly and traumatic. Similarly, many women whose cancers are detected by mammography still die of their disease. If mammograms saved lives, both breast cancer–associated mortality and total mortality in populations screened should decrease. This hypothesis has been tested in multiple trials.

As of 2011, the strongest evidence shows that any difference in **overall** mortality between populations exposed to screenings and those not screened is small: for every 2000 women invited for screening throughout 10 years, one will have her life prolonged; 10 healthy women who would not have been diagnosed if there had not been screening will be treated unnecessarily, and more than 200 women will experience important psychological distress for many months because of false-positive findings.[30]

In 2009, USPSTF changed its screening recommendations regarding breast cancer for women age 40 to 49. Previously recommending routine screening in this population, the Task Force now argued that the improvement in mortality in women between age 40 and 49 was small and that possible harms needed to be considered. Instead, USPSTF recommended that physicians discuss the risks and benefits of screening with the women and to proceed according to their risk/benefit preferences. This change led to a significant media backlash. Many people claimed the decision amounted to "care rationing," and that the USPSTF had overstepped its mandate by weighing mortality benefits against anxiety.[31] The Task Force argued that the evidence did not support a "one size fits all" recommendation and that their guidelines empowered patients and their physicians to make rational decisions based on evidence and more respectful of individual values.[32] As of 2012, the rating is a "B" for women age 50 to 74 (recommended) and a "C" for women 40 to 49, indicating that USPSTF believes the decision to screen should be individualized, and the net benefit is likely small.

Prostate Cancer

Prostate cancer affects men in a broad age range and has a wide variability in its impact on mortality; some are rapidly fatal, whereas others are slow-growing and indolent. False-positive results of prostate-specific antigen (PSA) testing are common and often lead to other unnecessary invasive testing (e.g., biopsy). This testing can then lead to diagnosis (often without a reliable way to distinguish between indolent and aggressive disease), treatment (e.g., surgery, radiation, and/or chemotherapy), and serious harm, including erectile dysfunction, bladder and bowel incontinence, and death, to manage a disease that might otherwise have never been problematic (most men die *with* prostate cancer, not *of* prostate cancer). To date, there is no compelling evidence that prostate cancer screening decreases all-cause or prostate cancer–specific mortality.[33] If there is any benefit, it likely accrues over more than 10 years. Therefore, USPSTF advised in 2012 against routine screening with PSA (D-rating).

Both these controversies illustrate the need of **personalizing** screening decisions. The decision to be screened for breast cancer or prostate cancer should be based on the patient's risk preferences and willingness to have false-positive test results and invasive follow-up testing. Many decision aids have been developed to help individuals make informed decisions.

They may delay medical visits that they might otherwise have made promptly. False-negative results also may falsely reassure clinicians. False-negative results can be detrimental to the health of the people whose results were in error, and if test results delay the diagnosis in people who have an infectious disease, such as tuberculosis, the screening tests can be dangerous to the health of others as well.

Overdiagnosis is another potential harm of screening programs. For example, screening mammography may lead to a diagnosis of a preinvasive lesion that is not invasive breast cancer (see Box 16-1). Actions taken in response to such findings, including surgery, may result in a scenario where the ostensible "cure" is in fact worse than the disease.

E. Bias in Screening Programs

It is not easy to establish the value of a community screening effort, unless a randomized controlled trial (RCT) is conducted. An RCT is needed to reduce the potential for bias. In cancer an association between screening and longer survival does not prove a cause-and-effect relationship because of possible problems such as selection bias, lead-time bias, and length bias.[5]

Selection bias may affect a screening program in different directions, all of which may make it difficult to generalize findings to the general population. On one hand, individuals may want to participate because they have a family history of the disease or are otherwise aware that they are at higher risk of contracting the disease. In this case the screening program would find more cases than expected in the general population, exaggerating the apparent utility of screening. On the other hand, individuals who are more "health conscious" may *preferentially* seek out screening programs or may be less likely to drop out.

Lead-time bias occurs when screening detects disease earlier in its natural history than would otherwise have

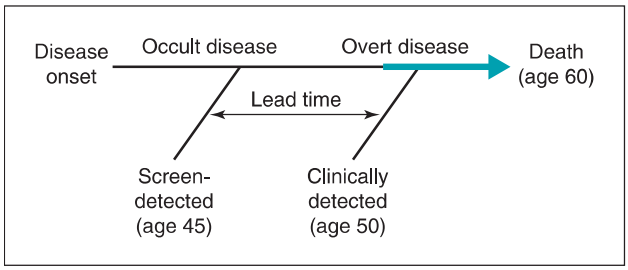


Figure 16-2 Lead-time bias. Overestimation of survival duration among screen-detected cases (relative to those detected by signs and symptoms) when survival is measured from diagnosis. This one patient survives for 10 years after clinical diagnosis and survives for 15 years after the screening-detected diagnosis. However, this simply reflects earlier diagnosis, because the overall survival time of the patient is unchanged. (From Black WC, Welch HG: Advances in diagnostic imaging and overestimates of disease prevalence and the benefits of therapy, *N Engl J Med* 328:1237–1243, 1993.)

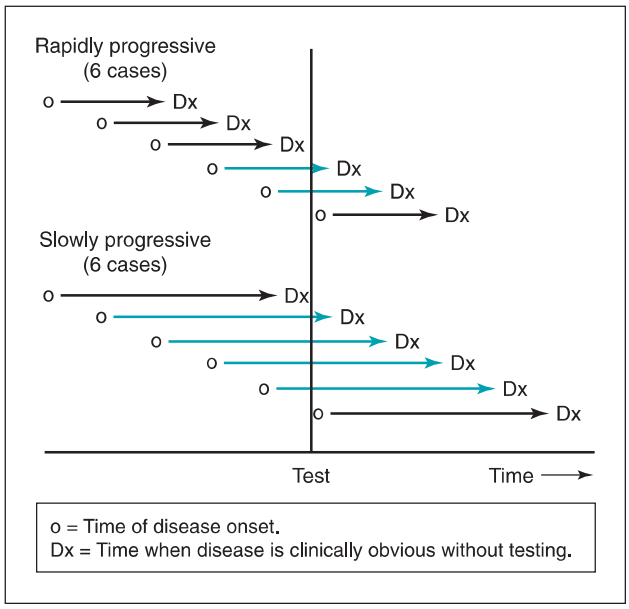


Figure 16-3 Overestimation of survival duration among screening-detected cases. This is caused by the relative excess of slowly progressing cases, which are disproportionately identified by screening because the probability of detection is directly proportional to the length of time during which they are detectable (and thereby inversely proportional to the rate of progression.) In these 12 patients, 2 of 6 rapidly progressive cases are detected, whereas 4 of 6 slowly progressive cases are detected. (From Black WC, Welch HG: Advances in diagnostic imaging and overestimates of disease prevalence and the benefits of therapy, *N Engl J Med* 328: 1237–1243, 1993.)

occurred, so that the period from diagnosis to death is increased. However, the additional *lead time* (increased time during which diagnosis is known) may not have changed the natural history of the disease or extended the longevity of life. This lead-time bias tends to operate in screening for cancers, no matter how aggressive the tumors (Fig. 16-2).

Length bias occurs when the full spectrum of a particular tumor, such as prostate cancer, includes cancers that range from very aggressive to very slow-growing. Individuals with slow-growing tumors live longer than individuals with the aggressive tumors, so they are more likely to be discovered by screening. Screening programs often select for the less aggressive, slower-growing tumors, and these patients are likely to survive longer after detection, regardless of the treatment given (Fig. 16-3).

Selection, lead-time, and length biases apply to both case finding and to community screening. Given the potential problems in showing the true effectiveness of screening, great care must be exercised to ensure a community screening program is worthwhile.

F. Repetition of Screening Programs

There are pitfalls in not carefully considering the details of repeat screening efforts. This is particularly true if an initial major screening effort is considered a great success, and enthusiasm may lead the organizers to repeat the screening too soon (e.g., 1 year later). Unless the population screened the second time is very different from the one screened the first time, a screening effort repeated after a short interval is likely to be disappointing. This is because the initial screening would have detected **prevalent cases** (cases accumulated over many years), whereas the repeated screening would detect only **incident cases** (new cases since the last screening), making the number of cases detected in the second screening effort smaller.[6]

Again, the more screening tests done on an individual, the more likely positive findings will occur, both true positive and false positive. If a woman begins annual breast cancer screening at age 40, she would undergo 30 screening mammograms by age 70. One study followed 2400 women age 40 to 69 for a 10-year period to determine the number of mammograms and clinical breast examinations done.[7] The women had an average of four mammograms and five clinical breast examinations during this decade, and almost one third had at least one false-positive examination. Recommending frequent repeat examinations carries a significant burden of cost and anxiety to rule out disease in individuals with false-positive examinations.

G. Simultaneous Screening for Multiple Diseases (Multiphasic Screening)

Multiphasic screening programs involve screening for a variety of diseases in the same individual at one point in time. Some investigators have argued that multiphasic screening makes community efforts more efficient. When a sample of blood is drawn, for example, it is easy to perform a variety of tests, using modern, automated laboratory equipment.

However, the yield of multiphasic screening is doubtful.[8] One problem is that multiphasic screening in an elderly population detects many diseases or abnormal conditions that have been found earlier and are already being treated, in which case funds are being used for unnecessary testing. Another problem is that multiphasic screening results in a relatively high frequency of false-positive results, which requires many participants to return for more expensive follow-up tests.

For each disease-free person screened with a battery of **independent tests** (tests that measure different values), the

Table 16-3 Correlation between Number of Screening Tests and Persons with False-Positive Result

No. of Screening Tests Performed*	Percentage of Persons with at Least One False-Positive Test Result†
1	5%
2	9.8%
4	18.5%
5	22.6%
10	40.1%
20	64.2%
25	72.3%

Data from Schoenberg BS: The "abnormal" laboratory result, *Postgrad Med* 47:151–155, 1970.
*It is assumed that the tests measure different values (i.e., the tests are independent).
†Percentages are based on tests that each has a 5% false-positive error rate.

probability that at least one of the screening tests would yield a false-positive finding can be expressed as $[1 - (1 - \text{alpha})^n]$, where alpha is the false-positive error rate (see Chapter 7) and n is the number of screening tests done. If two screening tests are performed and alpha is 5% (making the test specificity 95%), the probability of a disease-free person's being recalled for further testing is $[1 - (0.95)^2] = [1 - (0.9025)]$ = almost 10%. If four tests are performed, the probability is $[1 - (0.95)^4] = [1 - (0.8145)] = 18.5\%$. As Table 16-3 shows, if 25 tests are performed, more than 70% of disease-free individuals would return for unnecessary but often costly follow-up testing.

One study described a controlled trial of multiphasic screening in which one group of individuals received a battery of special screening tests that included hearing and vision tests, glaucoma screening, blood pressure measurements, spirometry, electrocardiography, mammography and breast examination, Papanicolaou smear, chest x-ray film, urinalysis, complete blood count, and 12 blood chemistry tests. Comparison of the findings in this group with the findings in a similar control group not subjected to the battery of tests (but receiving their regular care) found *no major differences* in the health knowledge, mortality rates, or morbidity rates of the two groups. The group who underwent multiphasic screening, however, spent more nights in the hospital.[9]

It is very difficult at present to integrate all recommended screening tests into a clinical encounter.[10]

H. Genetic Screening

Recent advances in genetic testing have made it more and more feasible to screen individual patients and populations for many different diseases. Indications for genetic testing may include **presymptomatic testing,** such as a patient tested for Huntington's disease. If the test is positive, patients are virtually certain of developing the disease over their lifetime. Alternatively, testing might be done to establish the predisposition for a disease, called **susceptibility testing.** This is the dominant form of testing for many common diseases, such as coronary artery disease (CAD). Most CAD cases follow a multifactorial pattern, with many different genes interacting with environmental factors to produce similar disease. For these diseases, the presence or absence of particular genetic traits can neither rule in nor rule out that the patient will develop the disease.[11]

However, the psychological impact of genetic test results on patients is often counterintuitive and poorly understood. So far, there is little evidence for significant adverse psychological impact, significant lifestyle changes, or screening adherence from consumer genetic testing.[12,13]

In contrast, **prenatal screening** has made a significant impact on population health for certain groups. This is particularly well established for individuals of Jewish Ashkenazi heritage, who have a significant carrier rate of "Jewish genetic disorders" (e.g., Tay-Sachs disease, familial dysautonomia) For this group, genetic testing combined with careful pretest and posttest counseling, has helped couples make informed decisions regarding their family planning. Such testing has also led to a decrease in the incidence of certain diseases.[14]

Several quality requirements beyond the accuracy of the test are specific to genetic screening tests. The genetic abnormality found must also correspond to a specific disease or increased risk for disease (**clinical validity**). Even if the test detects a genetic abnormality that meaningfully predicts disease, the information may not be useful to the patient (**clinical utility**).[15] For most genetic tests, there is little evidence of clinical utility, and the standards for analytic and clinical validity are much lower than for any other diagnostic test. Lastly, genomic screening seems to be predicated on the idea that the only way to change genetic vulnerability is through changing genes. In fact, gene expression is influenced by environmental stimuli, and lifestyle interventions may change gene expression.[16]

II. INDIVIDUAL CASE FINDING

A. Periodic Health Examination

Historically, the most common method of prevention in clinical medicine, especially for adults, was the annual physical examination (checkup), now known as the *periodic health examination.* After World War II the number of available treatments for chronic illnesses increased greatly, and more people began to have an annual checkup, usually consisting of a medical history, physical examination, complete blood count, urinalysis, chest x-ray film, and electrocardiogram. Despite the popularity of these checkups, the number of recipients was limited because many insurance plans would not cover their costs, although some corporations provided them as a benefit for high-level managers ("executive physicals"). Most research on the periodic health examination before the 1960s concerned examinations that were sponsored by businesses or industries or were conducted by the few large health plans existing at the time.

An annotated bibliography of 152 early studies of periodic health examinations showed that reports published before 1940 were mostly anecdotal and were enthusiastic about the examinations.[17] Reports between 1940 and 1962 were more likely to include quantitative data and, although still supportive, increasingly raised serious questions about routine use of examinations. The subsequent increase in the number of health maintenance organizations (HMOs) in turn increased the use of periodic examinations in larger populations. Although most investigators agreed that examinations in children were beneficial, increasingly the studies began to cast doubts about the cost-effectiveness of periodic health examinations in adults.[18-20]

During the 1970s, investigators began moving toward the idea of modifying the periodic examination to focus only on the conditions and diseases that would be most likely to be found in a person of a given age, gender, and family history. This approach was termed "lifetime health monitoring."[21] The greatest support for a new approach came in 1979, when the Canadian Task Force on the Periodic Physical Examination recommended that the traditional form of periodic checkup be replaced by the use of **health protection packages** that included gender-appropriate and age-appropriate immunizations, screening, and counseling of patients on a periodic basis.[22] Specifically, the Task Force recommended that "with certain exceptions, the procedures be carried out as case finding rather than screening techniques; that is, they should be performed when the patient is attending for unrelated symptoms rather than for a specific preventive purpose." Among the certain exceptions noted by the task force were pregnant women, the very young, and the very old, for whom they recommended regular visits specifically for *preventive purposes.*

B. Health Risk Assessments

Health risk assessments (HRAs) use questionnaires or computer programs to elicit and evaluate information concerning individuals in a clinical or industrial medical practice. Each assessed person receives information concerning his or her estimated life expectancy and the types of interventions that are likely to have a positive impact on health and longevity.

For many years, the idea of HRAs has been promoted by clinicians enthusiastic about detecting disease and risk factors in individuals. Based on the founders' original work, the Society for Prospective Medicine was formed,[23] to improve the construction and use of HRAs and the practice of preventive (*prospective*) medicine in a clinical or industrial medical practice.[24] Toward this end, the Society promotes the use of HRAs for the following:

- Assessing the needs of individual patients as they enter a medical care system or of employees in an industrial setting.
- Developing health education information tailored to the needs of the individuals who complete the assessment.
- Developing cost-containment strategies based on better acquisition of health risk information from individuals.

Most HRAs use questionnaires or interactive computer programs to gather data concerning each person being assessed. In addition to data such as height, weight, blood pressure, cholesterol level, and previous and present diseases, the information usually includes details concerning the person's lifestyle and family history. Using an algorithm, a computer calculates the person's "risk age" on the basis of the data. Most HRAs use an algorithm based on findings of the Framingham Heart Study. The **risk age** is defined as the age at which the average individual would have the same risk of dying as the person being assessed. If the assessed person's risk age is older than his or her chronologic age, that means he or she has a higher risk of dying than the average individual of the same chronologic age. Likewise, if the assessed person's risk age is younger than the chronologic age, the person has a lower risk of dying than the average individual of the same chronologic age.

The HRAs usually provide a printed report about the assessed person's relative risk of dying or risk age, combined with some sort of educational message regarding the types of interventions that would have the most positive effect on the person's life expectancy, if instituted. The printed HRA reports have become more sophisticated in recent years and are sometimes supplemented with individualized educational messages.

Studies have extensively evaluated HRAs, with mixed results.[25-27] Criticisms focus on errors or lack of information by the persons entering the data, difficulties in validating the predictions, uncertainties about the correct reference population for baseline risks, and limitations related to the instruments focusing mainly or exclusively on mortality and not on morbidity or the quality of life. The greatest strength of HRAs may be the ability to estimate disease levels at the population level, clarify how nutritional and lifestyle factors affect an assessed person's risk of death, and motivate the person to make changes in a positive direction. HRAs principally serve to *raise awareness,* which is just one of several domains, and generally not the most important, related to behavior change.[28]

III. SCREENING GUIDELINES AND RECOMMENDATIONS

The many organizations that issue screening guidelines and recommendations include the following:

- Specialty organizations (e.g., American Urological Association)
- Organizations representing primary care specialties (e.g., American College of Physicians, American Academy of Family Physicians)
- Foundations for the treatment and prevention of particular diseases (e.g., American Cancer Society)
- Organizations dedicated to evaluating screening recommendations (e.g., U.S. Preventive Services Task Force [USPSTF], American College of Preventive Medicine [ACPM], Canadian Task Force on the Periodic Health Examination)

In many cases, these organizations agree on their screening recommendations. However, certain diseases and screening methods have led to major controversy, such as breast cancer screening and prostate cancer screening. In general, the specialty organizations tend toward recommending screening methods related to their field, unless there is evidence of harm. In contrast, the ACPM and USPSTF tend to only recommend screening programs for which there is unequivocal evidence of benefits in patient outcomes. (See Box 16-2 and Chapter 18.)

In an effort to clarify many of the issues concerning screening and case finding and to make evidence-based recommendations, the U.S. Department of Health and Human Services created the **U.S. Preventive Services Task Force.** In its investigations, USPSTF reviews data concerning the efficacy of three broad categories of interventions:

- **Screening** for disease in asymptomatic clinical populations and in certain high-risk groups (secondary prevention)

Box 16-2 Lung Cancer Screening: Simulation Models, Stage Differences, and RCTs

The development of new diagnostic methods offers new screening possibilities. Conducting a randomized controlled trial (RCT) of a new screening intervention is arduous and time-consuming. In the absence of RCTs, preventive medicine practitioners sometimes rely on single-arm studies or mathematical modeling of screening interventions through cost-utility analysis (see Chapter 6). The history of lung cancer screening illustrates the pitfalls of such sources of evidence.

Lung cancer remains the number-one cause of cancer mortality in the United States. For a long time, there was no viable way to screen for lung cancer. Chest x-ray and sputum examination had been tested but only led to more invasive testing, with no difference in mortality. Then, helical computed tomography (CT) imaging became available and seemed to offer the capacity to find small lung cancer nodules early.[34] Several uncontrolled trials were performed and showed higher cancer detection rate.[35] Several authorities advocated to start screening immediately based on the difference in the distribution of cancer stages found in the screened group from that usually found in clinical practice; patients in the screened group were much more likely to be diagnosed with early and small, potentially curable cancers.[36] Several modeling studies of screening with helical CT were then published, with conflicting results.[37,38]

In 2002 the National Lung Screening Trial was launched. More than 53,000 participants were randomized to either three annual helical CT scans or chest x-ray films. In 2011 the results were published: There were 247 deaths from lung cancer per 100,000 person-years in the low-dose CT group and 309 deaths per 100,000 person-years in the radiography group, representing a relative reduction in mortality from lung cancer with low-dose CT screening of 20.0%.[39] Although less than expected by proponents, this mortality reduction was still clinically significant. However, the trial also likely showed evidence of overdiagnosis; even after the gap in detection time between the two screening modalities closed, the screened group had more cancer than the control arm.[40]

This example shows that modeling can inform decisions when no evidence is available. However, given the significant biases at work to have uncontrolled studies overestimate screening benefits, there is no alternative to rigorous RCTs.

- **Counseling** to promote good health habits and prevent disease (health promotion)
- **Immunizations** and **chemoprophylaxis** to prevent specific diseases (primary prevention)

The first report of the USPSTF was issued in 1989. Since then, there have been regular literature reviews and updated screening recommendations for the entire spectrum of diseases amenable to screening, counseling, and prophylaxis. Recommendations are upgraded regularly and are available online.[29]

IV. SUMMARY

The goal of secondary prevention is the detection of disease or risk factors in the presymptomatic stage, when medical, environmental, nutritional, and lifestyle interventions can be most effective. Screening is done in a community setting, whereas case finding is done in a clinical setting. To be beneficial and cost-effective, community screening programs must fulfill various requirements on the health problem to be detected, the screening test used, and the system available to provide health care for people with positive screening results. Selection, lead-time, and length biases can lead to overestimates of benefit from screening, particularly the program detecting cancer. Although multiphasic screening seeks to make the process efficient by searching for many conditions at the same time, the high incidence of false-positive results and associated problems have made this technique less successful than was originally anticipated. Genetic screening introduces a new subset of requirements for screening tests, including clinical validity and clinical utility.

Historically, the periodic health examination has been the most common method of case finding. Because of disappointing benefits, however, it is now being replaced by lifetime health monitoring. This approach focuses on monitoring individuals for the specific set of conditions and diseases most likely to be found in persons of a certain age and gender, and its use has been advocated by experts on preventive medicine in Canada and the United States. Many practitioners who emphasize preventive medicine prefer to see their patients for checkups more often than may be recommended, such as 1 or 2 years, to maintain a relationship of trust and to repeat health promotion messages that are important for efforts to change behavior.

References

1. Berwick DM: Screening in health fairs: a critical review of benefits, risks, and costs. *JAMA* 254:1492–1498, 1985.
2. Nelson HD et al: Screening for ovarian cancer: a brief update. http://www.uspreventiveservicestaskforce.org/3rduspstf/ovariancan/ovcanup.htm.
3. Nelson HD, Tyne K, Naik A, et al: Screening for breast cancer: an update for the U.S. Preventive Services Task Force. *Ann Intern Med* 151:727–737, 2009.
4. Elmore JG, Armstrong K, Lehman CD, et al: Screening for breast cancer. *JAMA* 293:1245–1256, 2005.
5. Bailar JD III: Mammography: a contrary view. *Ann Intern Med* 84:77–84, 1976.
6. Christopherson WM, Parker JE, Drye JC: Control of cervical cancer: preliminary report on a community program. *JAMA* 182:179–182, 1962.
7. Elmore JG, Barton MB, Moceri VM, et al: Ten-year risk of false-positive screening mammograms and clinical breast examinations. *N Engl J Med* 338:1089–1096, 1998.
8. Bates B, Yellin JA: The yield of multiphasic screening. *JAMA* 222:74–78, 1972.
9. Olsen DM, Kane RL, Proctor PH: A controlled trial of multiphasic screening. *N Engl J Med* 294:925–930, 1976.
10. Yarnall KS, Pollak KI, Østbye T, et al: Primary care: is there enough time for prevention? *Am J Public Health* 93:635–641, 2003.
11. Robin NH, Tabereaux PB, Benza R, et al: Genetic testing in cardiovascular disease. *J Am Coll Cardiol* 50:727–737, 2007.

12. Heshka JT, Palleschi C, Howley H, et al: A systematic review of perceived risks, psychological and behavioural impacts of genetic testing. *Genet Med* 10:19–32, 2008.
13. Bloss CS, Schork NJ, Topol EJ: Effect of direct-to-consumer genome-wide profiling to assess disease risk. *N Engl J Med* 364:524–534, 2011.
14. Gross SJ: Carrier screening in individuals of Ashkenazi Jewish descent. *Genet Med* 10:54–56, 2008.
15. Hogarth S, Javitt G, Melzer D: The current landscape for direct-to-consumer genetic testing: legal, ethical, and policy issues. *Annu Rev Genomics Hum Genet* 9:161–182, 2008.
16. Ornish D, Magbanua MJ, Weidner G, et al: Changes in prostate gene expression in men undergoing an intensive nutrition and lifestyle intervention. *Proc Natl Acad Sci USA* 105:8369–8374, 2008.
17. Siegel GS: *Periodic health examinations: abstracts from the literature*, Washington, DC, 1963, US Department of Health, Education, and Welfare.
18. Schor SS, Clark TW, Parkhurst LW, et al: An evaluation of the periodic health examination: the findings in 350 examinees who died. *Ann Intern Med* 61:999–1005, 1964.
19. Roberts NJ, Ipsen J, Elsom KO, et al: Mortality among males in periodic health examination programs. *N Engl J Med* 281:20–24, 1969.
20. Spitzer WO, Brown BP: Unanswered questions about the periodic health examination. *Ann Intern Med* 83:257–263, 1975.
21. Breslow L, Somers AR: The lifetime health monitoring program: a practical approach to preventive medicine. *N Engl J Med* 296:601–608, 1977.
22. Canadian Task Force on the Periodic Physical Examination: The periodic health examination. *Can Med Assoc J* 121:1193–1254, 1979.
23. Robbins LC, Hall J: *How to practice prospective medicine*, Indianapolis, 1970, Methodist Hospital of Indiana.
24. Society for Prospective Medicine: Managing health care, measuring lives: expanding the definition and scope of health risk appraisal. Thirty-First Annual Meeting of the Society for Prospective Medicine, New Orleans, 1995.
25. Foxman B, Edington DW: The accuracy of health risk appraisal in predicting mortality. *Am J Public Health* 77:971–974, 1987.
26. Schoenbach VJ: Appraising health risk appraisal (editorial). *Am J Public Health* 77:409–411, 1987.
27. Smith KW, McKinlay SM, McKinlay JB: The reliability of health risk appraisals: a field trial of four instruments. *Am J Public Health* 79:1603–1607, 1989.
28. O'Donnell MP: A simple framework to describe what works best: improving awareness, enhancing motivation, building skills, and providing opportunity. *Am J Health Promot* 20(1 suppl):1–7 (following 84, iii), 2005.
29. US Preventive Services Task Force. http://www.uspreventiveservicestaskforce.org/.
30. US Preventive Services Task Force: *Guide to clinical preventive services*, ed 2, Baltimore, 1996, Williams & Wilkins.
31. When evidence collides with anecdote, politics, and emotions: breast cancer screening. *Ann Intern Med* 152:531–532, 2010.
32. Gøtzsche PC, Nielsen M: Screening for breast cancer with mammography. *Cochrane Database Syst Rev* (1):CD001877, 2011.
33. Chou R, Croswell JM, Dana T, et al: Screening for prostate cancer: a review of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 155:762–771, 2011.
34. Kramer BS, Berg CD, Aberle DR, et al: Lung cancer screening with low-dose helical CT: results from the National Lung Screening Trial. *J Med Screen* 18:109–111, 2011.
35. The National Lung Screening Trial: overview and study design. NLST Research Team. *Radiology* 258:243–253, 2011.
36. Henschke CI: CT screening for lung cancer is justified. *Nat Clin Pract Oncol* 4:440–441, 2007.
37. Mahadevia PJ, Fleisher LA, Frick KD, et al: Lung cancer screening with helical computed tomography in older adult smokers: a decision and cost-effectiveness analysis. *JAMA* 289:313–322, 2003.
38. Bach PB, Jett JR, Pastorino U, et al: Impact of computed tomography screening on lung cancer outcomes. *JAMA* 297:1–9, 2007.
39. National Lung Screening Trial Research Team: Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 365:395–409, 2011.
40. Sox HC: Better evidence about screening for lung cancer. *N Engl J Med* 365:455–457, 2011.

Select Readings

Fletcher RH, Fletcher SW: *Clinical epidemiology: the essentials*, ed 4, Philadelphia, 2005, Lippincott, Williams & Wilkins.
Katz DL, Nawaz H, Greci L: *Clinical epidemiology and evidence-based medicine: fundamental principles of clinical reasoning and research*. Thousand Oaks, Calif, 2001, Sage.
Welch HG: *Should I be tested for cancer? Maybe not and here's why*, Berkeley, Calif, 2004, University of California Press.
Woolf SH, Jonas S, Kaplan-Liss E, editors: *Health promotion and disease prevention in clinical practice*, ed 2, Philadelphia, 2007, Lippincott, Williams & Wilkins.

Website

http://www.uspreventiveservicestaskforce.org/ [U.S. Preventive Services Task Force]