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EDITORIAL

H. GILBERT WELCH, MD, MPH
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Finding and Redefining Disease

Physicians have traditionally cared for the sick. Patients have sought our help to alleviate pain, ameliorate symptoms, and when possible, to cure disease. Over the past couple of decades, however, there has been increasing public pressure for the medical profession to pay more attention to the well. Specifically, we are being encouraged to prevent disease. Although this occasionally refers to persuading people to adopt a "healthy lifestyle" (e.g., exercise regularly, eat right, and avoid risky behaviors), more commonly it means that physicians are seeking disease in their patients.

Should the standards of evidence be different for interventions targeting the well? I think so. Although our symptomatic patients generally ask for help, asymptomatic people are being told that they need our help. When suffering patients call for help, it seems reasonable to act with a lower standard of literature-based proof. The demand for proof is further reduced when direct evidence of the intervention's usefulness, albeit circumstantial, may be provided from the patient's response to therapy (i.e., whether symptoms persist or resolve). For people who are well, however, benefit cannot be observed directly because the expectation is that most people will stay well regardless of what is done. Instead, there is an implied pledge made to individuals who are well,[1,2] a pledge that services delivered now will prevent disease in the future. The burden of proof must lay with proponents of early detection to demonstrate that it works.

In this issue of **ecp**, Black makes it clear how much the quality of the evidence matters.[3] He reminds us how cursory evaluations of screening are subject to some of the most powerful biases in medicine and may lead to dramatically wrong conclusions (*see* **Primer**). The combined effect of lead-time, length, and overdiagnosis biases can make negative effects seem to produce survival benefit. In short, early detection could actually harm people while appearing to help.

The randomized trial must be the fundamental standard to demonstrate that early detection can provide net benefit. Only a randomized trial can disentangle the real from the apparent effects. As Black points out, however, randomized trials have serious limitations of their own. One obvious limitation is generalizibility—a trial provides a test of screening under well-specified conditions, whereas clinical practice may be more haphazard. Another is the need for large numbers of study participants. Black argues that

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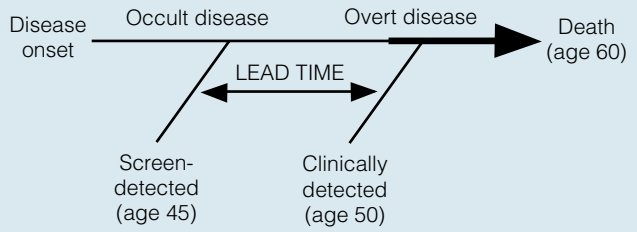
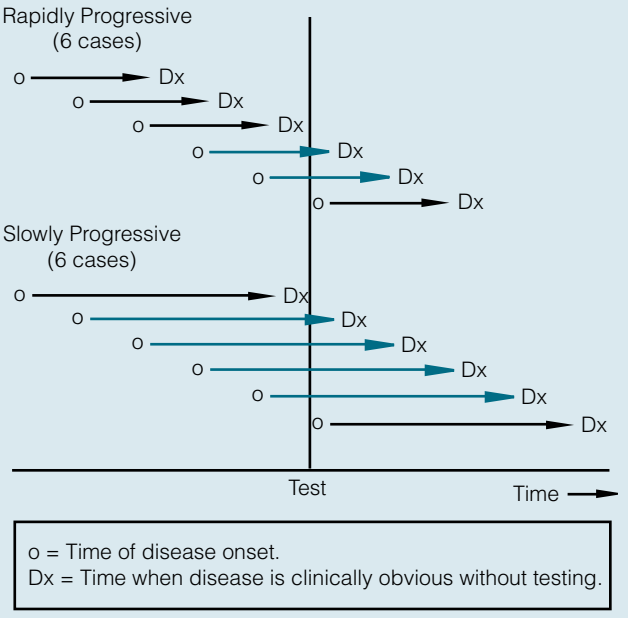
Primer on Lead-Time, Length, and Overdiagnosis Biases

The apparent effects of early diagnosis and intervention (measured in terms of how screening-detected cases compare with cases detected by signs and symptoms) are always more favorable than the real effects (measured in terms of how a population that is screened compares with a population that is not). The comparison between screening-detected cases and others overestimates benefit because the former consists of cases that were diagnosed earlier, progress more slowly, and may never become clinically relevant. This comparison, therefore, is said to be *biased*. In fact, three biases exist that inflate the survival of screen-detected cases.

1. 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. In the figure below (representing one patient), the 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.



2. Length bias: Overestimation of survival duration among screening-detected cases caused by the relative excess of slowly progressing cases. These cases 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 the following figure (representing 12 patients), 2 of 6 rapidly progressive cases are detected, whereas 4 of 6 slowly progressive case are detected.



3. Overdiagnosis bias: Overestimation of survival duration among screen-detected cases caused by inclusion of *pseudodisease*—subclinical disease that would not become overt before the patient dies of other causes. Some researchers further divide pseudodisease into two categories: one in which the disease does not progress (type I) and another in which the disease does progress—but so slowly that it never becomes clinically evident to the patient (type II). Inclusion of either type as being a "case" of disease improves apparent outcomes of screening-detected cases.

evaluations of screening will ultimately need to be based on a combination of trial data and decision modeling. Perhaps the best we can expect is to have the real effect of an early detection strategy demonstrated under a few well-specified conditions and then make careful inferences about how changing conditions (e.g., target population, screening frequency, new tests) will affect net benefit.

At first glance, there is every reason to believe that early detection should work. If people are examined carefully enough by using advanced laboratory or imaging technologies, then most disease ought to be "caught" at an early stage. It also stands to reason that disease found earlier will be easier to treat. Consequently, much of the mortality and morbidity of advanced disease should be preventable. The idea of early detection is so appealing that there has been a dramatic growth in the use of diagnostic tests—as part of systematic efforts (the **Appendix Table** provides the current cancer screening recommendations of the U.S. Preventive Services Task Force and the American Cancer Society) or as more routine testing in general (witness the finding, also in this issue, that one quarter of the elderly in Miami undergo echocardiography each year[4]).

But there are downsides to early detection. First, many people must be involved but only a few can benefit. To encourage people to be screened, proponents must articulate a message that motivates people to do so (exemplified by the "1-in-9" statistic for breast cancer). Too often this persuasion involves overstating the risk for the target disorder and exaggerating the potential

benefit of screening. In an effort to find the few, a sort of "dis-ease" is spread across the population.

Second, early detection identifies more people as being sick. To find cases earlier, the threshold for making the diagnosis must be lower. The "advance" in diagnostic testing is the ability to find disease that was previously undetectable. Not surprisingly, advanced diagnostic tests invariably find more cases. The problem is larger than the familiar one of false-positive test results—it includes true-positive results where the "disease" identified has uncertain significance (as evidenced by the large reservoir of undetected thyroid,[5] breast,[6] and prostate[7] cancers). There will be some patients who would never become aware of their disease were it not for the test. In short, there may be people who previously felt healthy and are being unnecessarily informed that they are sick.

Also in this issue of **ecp**, Schwartz and Woloshin[8] demonstrate just how ubiquitous disease could become. Using the National Health and Nutrition Examination Survey, they calculated the impact of new disease definitions on the number of Americans who have four common conditions: diabetes, hyperlipidemia, hypertension, and obesity. The bottom line is that three out of four adults meet the criteria for one of these conditions. After digesting these data, some of you may not feel so well. (I myself thought seriously about a new diet.)

Third, early detection strategies imply that more people will be treated. Some can benefit—those whose disease is both 1) destined to cause morbidity and mortality and 2) not as effectively treated once it becomes clinically evident. Some will be treated unnecessarily—either because their disease was always destined to remain subclinical or because later treatment would have worked just as well. Others will be harmed—those for whom the potential risks (however rare) of unnecessary treatment become a reality.

Finally, the potential exists for early detection to become distracting to clinicians.[9] Consider how the interest in measuring quality interacts with the focus on prevention. Measures of prevention are easily understood and have wide appeal. Moreover, they are relatively easy to obtain. It is clearly easier for health plans to measure how well providers comply with screening recommendations than it is to determine how good they are in helping sick patients. Similarly, it is easier to improve physician compliance on an agreed-on preventive goal than it is to improve the quality of care given the sick. But that doesn't mean that prevention should become the focus of health care. Although all physicians would like to see more disease prevented, we should ask ourselves if the focus on finding early disease is distracting us from caring for the sick.

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APPENDIX TABLE

Current screening recommendations of the U.S. Preventive Services Task Force and the American Cancer Society

SCREENING STRATEGY	U.S. PREVENTIVE SERVICES TASK FORCE*		AMERICAN CANCER SOCIETY†	
	AGE *(yr)*	FREQUENCY	AGE *(yr)*	FREQUENCY
Colorectal cancer				
Fecal occult blood testing	50+	Yearly	50+	Yearly
		and/or		and
Sigmoidoscopy	50+	Periodically (unspecified)	50+	Every 3–5 years
				or
Colonoscopy	Insufficient evidence to recommend for or against		50+	Every 10 years?
				or
Double-contrast barium enema	Insufficient evidence to recommend for or against		50+	Every 5–10 years
				and
Digital rectal examination	Insufficient evidence to recommend for or against		50+	At the same time as above tests
Prostate cancer				
Digital rectal examination	Not recommended		50+	Offer yearly
Prostate-specific antigen				
General population	Not recommended		50+ (if expected to live ≥ 10 years)	Offer yearly
High-risk men‡			45+ high risk	Offer yearly
Cervical cancer				
Papanicolaou test	18–65 (sexually active)	Every 1–3 years	18+	Yearly for 3 years then MD choice
Breast cancer				
Mammography	40–49	Insufficient evidence	40–49	Yearly
	50–75	Every 1–2 years	50+	Yearly
				and
Clinical breast examination	May be added to mammography		20–40	Every 3 years
			40+	Yearly
				and
Self breast examination	Insufficient evidence to recommend for or against		20+	Monthly
Skin cancer				
Complete skin examination	Insufficient evidence to recommend for or against		20–39	Every 3 years
			40+	Every year

**U.S. Preventive Services Task Force. Guide to Clinical Preventive Services, 2d ed. Baltimore: Williams & Wilkins; 1996.*

†Summary of American Cancer Society Recommendations for the Early Detection of Cancer in Asymptomatic People. 1998 American Cancer Society World Wide Web Page (www.cancer.org).

‡Family history for prostate cancer (≥2 first-degree relatives); African-American.

Correction: Omitted Author

Marjorie Cypress, CNP, CDE, an important member of the Diabetes Episodic Care Group, was inadvertently omitted as an author from a recent article.[1]

1. Friedman NM, Gleeson JM, Kent MJ, Foris M, Rodriquez DJ. Management of diabetes mellitus in the Lovelace Health Systems' EPISODES OF CARE Program. Effective Clinical Practice. 1998;1:5-11.

Correction: Incorrect Degrees

In a recent article,[1] PhD was mistakenly added to an author's name (P Churgin).

1. Churgin P, Strawn K. Population health management with computerized patient records. Effective Clinical Practice. 1998;1:61.