Bridge Across the Abyss

Bridge Across the Abyss: Medical Myths and Misconceptions

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For my parents and two brothers

For my patients; past, present and future

"Life is short and the art of medicine long and difficult.
Knowledge is important but experience fallacious.
The physician must not only be prepared to do what is right,
but must see that others involved in the care of patients
also do what is right."

— *Hippocrates*

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I began to work on *Bridge across the Abyss* in December 2006. The book was written sometimes at home in Lexington, sometimes while enjoying the hospitality of friends and family in the Middle East.

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Introduction

There is a line that has haunted me for many years in an essay on Leonardo da Vinci by the great early 20th century French poet Paul Valéry (1871–1945). In his 1895 essay entitled *Introduction à la méthode de Léonard de Vinci* or *Introduction to the method of Leonardo da Vinci,* there is an eloquent description of da Vinci's mind in its prowess and elegance; Valéry says that the Italian artist could not but think of a bridge whenever he thought of an abyss. Metaphorically, an abyss is the equivalent of what is presented to us as immutable, definitive, impossible to go beyond. No matter how deep and problematic the scene that presented itself to him, Leonardo da Vinci always had the capacity to think of some alternative to it, some way of solving the problem, some gift for not passively accepting what was given to him, as if the scene that Leonardo imagined could always be envisioned in a different, and perhaps more hopeful, way.

Few of us would dare to compare ourselves with the genius that was Leonardo. Notwithstanding, it is important to realize that the advantages of education in general and medical education in particular is that, quite apart from giving us methods and skills for dealing with areas of experience, they also give us the opportunity to see things differently, and to try in our own way to construct our own bridges. Indeed, knowledge is power. But there is more to knowledge than the mere amassing of information. Jean-Paul Sartre once said about a friend who had studied at France's greatest scientific college, the Ecole Polytechnique: "My friend is really incredibly brilliant. He knows everything. But that is all he knows." I would qualify my previous statement as knowledge plus action is power.

Far from being a kind of automatic rejectionism, skepticism is the first step in trying to build a structure across an abyss. That quality is what separates outstanding from mediocre education. If physicians cannot inspire their medical students to do that, if they cannot somehow move them to grasp that education is really self-education and that residency training is what one makes of it and not the unquestioning accep-

tance of what in the end authority says, then future physicians have been committed to intellectual and ultimately moral helotry.

There is nothing about our time now that is more dispiriting than intellectual servitude. Aside from the monotonous pre-packaged news and information that we are bombarded with without respite, alas, the situation is similar even in most academic and intellectual discussion, and sadly, even in medicine, where a steady diet of received ideas compel most people into acceptance of dictated principles proclaimed by one public health authority or another. What I am talking about here is the opposite of that, namely intellectual restlessness: you refuse to accept what orthodoxy or dogma tell you is the truth, and seek in your way to understand things so as to change them, to make them yours. That, in essence, is the cornerstone of creative ingenuity.

Paradoxically, medical education often asks of physicians to serve and submit to authority — the authority of tradition, of learning itself, of the medical scholars and scientists who went before them and in a sense made them possible — and, at the same time, doctors must somehow remain critical. However, what makes one defiant is a belief in a great idea, namely the idea of emancipation, the idea of enlightenment, which of course is where the bridge leads you. As a medical student and as a resident, I tried to challenge what I heard from my peers often and this actually provided a lot of fodder on which this book thrived. There are many risks, of unpopularity, of being isolated, of being reviled as a consequence of what I write here. But in the final analysis, there is nothing more noble than to risk all those things in order to be able to build that bridge.

This book is a discussion of various medical myths that describe commonly employed clinical practices that are instituted and taught despite the surprising lack of data supporting their use. In essence, these have created a medical dogma that is seldom questioned and accepted as valid regardless of what the evidence has borne out. The desperate need to focus on the basics (common things are common), and the equally crucial need to emphasize critical thinking, reflexive cynicism and refutationist inquisition have inspired me to write this book. The epigraphic quote on the front page notwithstanding, it is not my intention to speak ill of doctors. Where it seems like I am, I hope it is clear that I have not

spared myself the same ironies. On the contrary, I believe that the seemingly inevitable promulgation of unsupported canards has everyone to blame — patients, doctors, nurses, public health authorities, nutritionists, and the lay press among others. If all of the preceding professionals are willing to give up conventional wisdom after it is overturned by scientific evidence, then this book is for them.

Ultimately, I hope my effort here will serve to optimize clinical practice, management and decision-making among members of the medical community in addition to empowering patients and contributing to their ability to become actively engaged in management decisions that may affect their care. I do not propose embracing other medical schools of thought as opposed to Western medicine — I am merely trying to enhance our understanding of what we already know.

My motivation in this effort is twofold. Patients are primarily my utmost concern. Better practice should lead to better outcomes. If you are a patient then I urge you to consider the presented information when you sit down and discuss your health concerns with your doctor. Secondly, providing a basis for inquisitive learning and critical thinking is imperative if medical education and ethics are to prevail over passive docility.

There is an undeniable abundance of dogma that is practiced without evidence-based clinical guidelines or alternatively, in spite of their existence. This needs to be challenged. Additionally, in some cases, guidelines suggestive of alternative practice do exist but are unfortunately ignored.

The book will be divided into eight chapters. In succession, I examine the increasingly prevalent notion of ever popular screening tests, the misguided approach to blood transfusion, the myths about cholesterol and heart disease, unfounded fears about anesthesia and pain killers, the inadequate use of stomach acid reducers, why we should not attempt to get rid of a patient's fever, and the billion dollar scam of multivitamin and supplement endorsement. Additionally, there is a glossary that discusses basic statistics used to interpret clinical trials and an epilogue that presents a brief history of evidence-based medicine. With the exception of the last chapter, several chapters open with some interesting historical perspective. Even though I really have never embraced the study of history solely as a way to avoid the mistakes of the past — it is a fruitless enterprise — for mistakes are inevitable. It follows that it is unreasonable to expect perfection. What is reasonable is that we never cease to strive for it.

Undoubtedly, I will sometimes be criticized for not offering alternatives and for being too negative. But everything I write here is premised

on the idea that what we have before us is a bad alternative or suboptimal thinking. To expect me, or any single individual, to provide ready-made, easy solutions is part of the mythical deformation that is disconcerting. Meeting the determined, even obsessive need for thinking anew by all of us is the goal here. The required stance of the intellectual as well as the scientist is that of the persistent skeptic who relentlessly questions dogmas in the classic Popperian style of critical rationalism.

This style turns the need for change to actually cause change. Whether you like that style or not, whether you agree with it or not, I ask that you at least recognize that I truly believe in it. For it alone, is the key to building *un ponte sull'abisso*, the bridge across the abyss.

Chapter One

To Screen or Not to Screen: Earlier is Not Always Better

Most of us have received the widely used skin test called the PPD (purified protein derivative) or Mantoux test to screen for exposure to tuberculosis. Health care providers may screen for depression using questionnaires such as the Beck Depression Inventory. Alpha-fetoprotein screening is used in pregnant women to help detect certain fetal abnormalities as part of so-called triple screening. Cancer screening attempts to diagnose disease in its early stages, such as using Pap (Papanicolaou) smears to detect cervical cancer, or mammography to detect breast cancer. The ever-growing list of screening tests laid out by many medical societies is as long as my arm; undoubtedly a great deal is invested in research that is the driving force behind the development of new tests. The types of trials considered "gold standard" (i.e. randomized double-blind placebo-controlled trials) may be expensive, so that funding sources play a role in what gets investigated. For example, public authorities may tend to fund preventive medicine studies to improve public health as a whole, while pharmaceutical companies fund studies intended to demonstrate the efficacy and safety of particular drugs.

Nowhere is the steadfast advocacy of contentious screening tests more apparent than in the offices of family practitioners and internists who practice primary care medicine. While traditionally known for their remarkable capability of producing monstrously detailed patient history and physical exam records and engaging in nuanced thought, many internists recommend screening without thinking about the negative consequences. A glance at any outpatient medical record today often has a list of the various tests laid out a la carte like a menu from Applebee's. It puzzles me that it seems that the doctor's job is now reduced to merely going down that list and simply regurgitate recommendations. But it's not as simple as they would have you believe.

Suppose you are a doctor. You are in an examination room of your clinic — one of those cramped spaces with bright fluorescent lights, a "Stop Smoking" poster and eye chart on the wall, a box of latex gloves on the counter right next to a standard sink with a foot pedal and a cold, padded patient table as centerpiece — seeing a female patient in her forties. She is a mother of three and is an accountant at a local bank. Despite the circumstances, and the flimsy gown she is in, she manages to maintain her composure. You feel no masses or abnormalities in her breasts. She had a screening mammogram before seeing you, and now you review the radiologist's report, which reads, "There is a loosely grouped localization of punctuate, clustered calcifications in the upper outer quadrant of the right breast." Translation: worrisome features, this could mean breast cancer. What do you do?

Screening is a strategy used to identify disease in an unsuspecting population. Unlike most medicine, in screening, tests are performed on those patients without any clinical indication or symptoms of disease. There is a prevailing conviction that earlier diagnosis is better. I suspect that this is not due to sheepish submission to the popular press and media outlets that perpetuate this belief or even to the private conversations held between primary care doctors and their patients in the outpatient clinic every day in this country. Instead, it is likely a result of that notion's intuitive appeal. It seems instinctively appropriate. In fact, questioning it has receded so dramatically in the public mind as to be non-existent.

The controversy that persists is essentially a direct effect of the emerging screening modalities that have enabled us to detect disease at earlier stages than we could have previously. Unfortunately, a more objective look at screening discloses some adverse consequences of our success.

The intention of screening is clear: to identify disease in a community early, thus enabling earlier intervention and management in the hope to reduce mortality and suffering from a disease. There is no question that screening may lead to an earlier diagnosis. The issue is whether it actually makes a difference. Moreover, there is no question that not all screening tests have been shown to benefit the person being screened; overdiagnosis, misdiagnosis, exacerbated anxiety, unnecessary procedures and evaluation and creating a false sense of security are some potential negative effects of screening. For these reasons, a test used in a screening program, especially for a disease with low incidence, must have good specificity in addition to acceptable sensitivity. More importantly,

it must have an effect on mortality, meaning it must be shown to increase survival in the screened patients. It's not enough to prove that a particular blood test or CT scan really spots cancer, for example. If I am a patient, I also need to know whether early detection of that cancer would make a difference in my ability to respond to treatment or it merely means that I would die at the same point but learn about my illness earlier than I would have without the test.

Screening for cancer sometimes detects low grade tumors that would never have presented clinically with symptoms. This was illustrated in a randomized trial of screening for lung cancer. There was an excess of 46 cancers diagnosed in the screened group over the control group (206 versus 160); these 46 were early stage cancers that were resected, but despite 11 years of follow up their counterparts never appeared as more advanced cancers in the control group, and there was no reduction in lung cancer mortality in the screened group. Do you really want to know that you have fatal lung caner if there is no evidence to suggest that anything can be done about it?

Virtually all medical organizations and societies have made recommendations about screening for various diseases and they sometimes disagree. The message is not consistent. Perhaps more interesting is the World Health Organization's 1968 guidelines on the principles of screening that are still applicable today:

1. The condition should be an important health problem.
2. There should be a treatment for the condition.
3. Facilities for diagnosis and treatment should be available.
4. There should be a latent stage of the disease.
5. There should be a test or examination for the condition.
6. The test should be acceptable to the population.
7. The natural history of the disease should be adequately understood.
8. There should be an agreed policy on who to treat.
9. The total cost of finding a case should be economically balanced in relation to medical expenditure as a whole.
10. Case-finding should be a continuous process, not just a "once and for all" project.

When studying a screening program using case-control or, more usually, cohort studies, various factors can cause the screening test to appear more successful than it really is. A number of different biases, inherent in the study method, will inevitably skew results.

Lead time bias

By screening, the intention is to diagnose a disease earlier than it would be without screening. Without screening, the disease may be discovered later once symptoms appear.

Even if in both cases a person will die at the same time, because we diagnosed the disease early with screening, the survival time since diagnosis is longer with screening. However, no additional years of life has been gained (and indeed, there may be added anxiety as the patient must live with knowledge of the disease for longer).

Looking at raw statistics, screening will appear to increase survival time (this gain is called *lead time*). If we do not think about what *survival time* actually means in this context, we might attribute success to a screening test that does nothing but advance diagnosis. In other words, I may die at 75 from lung cancer but finding out about my cancer at 60 instead of 65 would not add 5 years to my life.

Length bias

Many screening tests involve the detection of cancers. It is often hypothesized that slower growing tumors have better prognosis than tumors with high growth rates. Screening is more likely to detect slower growing tumors (due to longer pre-clinical sojourn time), which may be less deadly. Thus screening may tend to detect cancers that would not have killed the patient or even been detected prior to death from other causes.

Selection bias

Simply put, not everyone will partake in a screening program. There are factors that differ between those willing to get tested and those who are not.

If people with a higher risk of a disease are more eager to be screened, (for instance a woman with a family history of breast cancer seeking to get a mammogram) then a screening test will look worse than it really is. This is because there are going to be more people with the illness joining, and a higher chance of people dying of that illness.

Selection bias may also make a test look better than it really is. If a test is more available to young and healthy people (for instance if people have to travel a long distance to get checked for disease) then fewer people in the screening population will get ill, and the test will seem to make a positive difference.

Overdiagnosis bias

Screening may identify abnormalities that would never cause a problem in a person's lifetime. An example of this is prostate cancer screening. It has been said that most men die with prostate cancer, not from it. Autopsy studies have shown that a high proportion of men who have died in other ways, have had prostate cancer when the prostate is examined under a microscope.

Aside from issues with unnecessary treatment (prostate cancer treatment is by no means without risk), overdiagnosis makes a study look good at picking up abnormalities, even though they are sometimes harmless.

Avoiding bias

The natural desire for quicker answers and cheaper studies is typically at odds with the desire for ideally valid and reliable measures of effectiveness and safety. While the selection of less definitive endpoints may allow for shorter trials and easier measurement, they may not yield useful information about how well an intervention saves or prolongs lives. Whenever less than ideal endpoints are selected, important questions will be left unanswered. This means that further trials will be necessary — requiring more time, more money, and more patient participation. Such a waste of resources can be avoided by selecting, at the outset of testing, outcomes that provide the clearest indications of the true efficacy and harms of the intervention being examined.

The only way to completely avoid these biases is to use a randomized controlled trial. These need to be very large, and very strict in terms of research procedure. It is not quick to do this type of research, and it is often expensive. However, when done rigorously, these are undeniably the best studies for assessing whether a screening test will increase a population's health.

Because survival is the most important issue for most patients, *mortality* is the major or *primary outcome* of interest. From this perspective, the best test for any intervention would follow study participants to compare the mortality rates between those exposed to the intervention to those not exposed at pre-specified time points into the future. Measures of *mortality* and *survival* track the success of an intervention in preventing cancer deaths. Mortality rate is expressed as the *number of deaths* in a certain period of time per standard unit of population. Survival usually refers to the *number of people alive* for a given period after an intervention.

Because mortality and survival are critical, easily measured, and objective endpoints, and because they can allow researchers to detect both beneficial and harmful effects of an intervention (decreases and increases in deaths), they are usually considered the preferred method for measuring efficacy in clinical trials of screening tests. In some studies, however, their usefulness as single endpoints would be limited. For example, mortality would not be a useful endpoint in trials where few deaths are expected, or where the interventions under investigation are expected to have small or moderate effects. Similarly, for cancers where most patients live well beyond the time of diagnosis and/or trial participation, it can take many years to gather sufficient data on mortality or survival to accurately assess an intervention. In such cases, interim endpoints can be important, but survival data must still be collected in order to fully assess the ultimate usefulness of the intervention. This should also be expected when trends in interim outcomes lead to a decision to end a trial early.

Mortality or survival endpoints might be based only on deaths resulting from, say, breast cancer *(cause-specific mortality)* or on all deaths in the study population regardless of cause *(all-cause or overall mortality)*. All-cause mortality can be a particularly useful outcome measure where interventions might have both beneficial and harmful effects. For example, the intervention may decrease breast cancer mortality but increase endometrial cancer mortality. As long as the cause of death is accurately assessed, both of these results would be discovered. *Misclassification error* occurs when the cause of death among trial participants is incorrectly identified, leading to inaccurate conclusions about the effect of the intervention on mortality or survival. Suddenly, randomized trials of screening tests are not so trivial.

In the 2002 issue of the *Journal of the National Cancer Institute*, Black and colleagues presented an important analysis of methodological pitfalls associated with randomized studies of screening interventions. The authors compared disease-specific and all-cause mortality from the 12 published randomized trials of cancer screening for which these endpoints were available. In 7 of the 12 studies, major inconsistencies were detected in the direction or magnitude of these two outcomes. In any screening study (or in the population to which its results are applied), the risk of the screened population dying of the target disease is low. Even if screening is "effective" in detecting disease in a phase at which it is still curable, a large number of subjects must be evaluated, and a substantial number of those must be treated to save one life from cancer. Although

modern diagnostic tests and even cancer operations appear to be remarkably safe, rare fatal complications do occur, and more subtle effects to hasten death through cardiovascular or other causes may be missed completely. Thus, there may be a fine balance between benefit and harm from screening. Their analysis provided a strong argument for the use of all-cause mortality as the primary endpoint in screening trials. Notwithstanding, disease-specific mortality rather than all-cause mortality has been the accepted end point of screening studies because fewer patients are required to provide adequate power (which is the probability of detecting an effect in the treatment versus control group if a difference actually exists. This probability increases with sample size). It has been assumed that disease-specific mortality is a good surrogate endpoint for all-cause mortality, but the study essentially raises serious doubts about the validity of this assumption. Whether measured directly or not, a decrease in all-cause mortality should be the ultimate aim of screening programs. In other words, a death from a nonmalignant cause is just as important as a cancer-related death.

What is the feasibility of all-cause mortality as a primary endpoint? The 7 studies assessed in the article by Black were about screening mammography for breast cancer. Because screening mammography is widely available in Western countries, performing a randomized study without substantial interference in the observed (control) arm may now be impossible. Therefore, careful attention needs to be paid to the available data. Some caution should be exercised in interpreting all-cause mortality in studies that were not prospectively designed to address this endpoint. Thus, as acknowledged by the authors, some of the inconsistencies observed may be the result of chance alone. Nonetheless, the studies concluded that breast cancer screening does not reduce all-cause mortality, a very controversial assertion that has sparked debate in both the lay and scientific press.

Alas, population-based screening trials that are designed with improvement in all-cause mortality as the primary endpoint will require very large numbers of patients, lengthy follow-up, and great expense. Still, we cannot justify implementation of screening programs that are costly to the individual and to the community if we are uncertain of their true benefit. Large randomized trials with mortality endpoints should be conducted to establish and quantify any benefit.

Breast Cancer: The controversy continues

Breast self-examination is yet another example of the failure to apply scientific rigor to screening. It has been widely advocated on an assumption that it must be beneficial and cannot do harm, which is untrue. Breast self-examination was shown in a recent large trial and meta-analysis from Shanghai (266,000 patients) to be ineffective (the malignant breast lumps are presumably noticed anyway on washing and dressing). But it caused harm: the self-examination group had more surgical biopsies (3,627 versus 2,398) and undoubtedly more anxiety. This result should discourage those practices. Another study conducted in St. Petersburg, Russia and published in 2003 included 123,748 patients and showed no effect on mortality.

As co-author of *Breast Cancer* and co-editor of *History and Advancement of Anastrozole in the Treatment of Breast Cancer*, and chair of the Psychosocial Oncology Committee at the National Cancer Research Institute, Dr. Michael Baum knows his stuff. He remarks in a recent interview, "In breast cancer, the mantra has always been 'catch it early and you'll save your life' or 'your life in your hands', clichés like that. This hypothesis, that women who regularly practice breast self-examination will have a lower mortality for breast cancer than those who don't, has been tested — and it doesn't hold up. There have been three large-scale trials — one in Shanghai, one in St. Petersburg, another in the United Kingdom — where they compared the outcome of women who had been trained and monitored in breast self-examination with those who had been left alone. And as far as breast cancer mortality was concerned, there was no difference. *But* there was twice the number of unnecessary surgical interventions among the women who practiced breast self-examination, among those who were more "aware", more cautious. This has even provoked the publication of the Canadian Medical Association to publish a paper and a leader which argued that as far as public health is concerned, breast self-examination has now been downgraded from Category C — unproven — to Category D: proven to be harmful."

Although there is a reasonably strong consensus that screening for breast cancer saves lives among women aged 50–69, debate is pretty fierce about the effect in women aged 40–49. The debate is particularly strong in the United States and Canada. The American Cancer Society, American Medical Association, and American College of Radiology recommend that screening should begin at age 40, whereas the United States Preventive Services Task Force, American College of Physicians, and Ca-

nadian Task Force on the Periodic Health Examination all recommend starting at age 50. In 1993, the United States National Cancer Institute stepped back from its recommendation to begin at age 40 after reviewing the most up to date data from the seven randomized trials conducted in Scotland, Sweden, the United States, and Canada. The report of the institute's international workshop concluded: "For (women aged 40–49 years) it is clear that in the first five to seven years after study entry, there is no reduction in mortality from breast cancer that can be attributed to screening. There is an uncertain, and if present, marginal reduction in mortality at about 10–12 years. Only one study (Health Insurance Plan) provides information on long term effects beyond 12 years, and more information is needed."

In January 1993, with four more years of follow up from these trials available, the National Institutes of Health convened a consensus development conference on breast cancer screening in women aged 40–49. After reviewing the literature and hearing presentations from 32 experts, the independent panel concluded that "at the present time, the available data do not warrant a single recommendation for mammography for all women in their forties. Each woman should decide for herself whether to undergo mammography. Given both the importance and complexity of the issues involved in assessing the evidence, a woman should have access to the best possible information in an understandable and usable form."

The dilemma for women in their 40s is that randomized trials of breast cancer screening have, on the one hand, found slower and smaller benefits and, on the other, found more frequent adverse effects than in older women. A meta-analysis found that, whereas mortality from breast cancer decreased among older women by about a third within seven years of study entry, mortality in screened and control groups among younger women was almost identical throughout the first seven years. Recently, a repeat meta-analysis, with 10–15 years of follow up data, found a 15% reduction in mortality among younger women invited for screening. (ratio=0.85, 95% confidence interval 0.71 to 1.01).

Why the slow and small benefit? At the consensus conference, Tabar presented data suggesting that some cancers in younger women spread faster and argued that younger women must be screened yearly for optimal effect. Others have pointed out that all trial analyses are done according to age at entry, not age at diagnosis. Because the incidence of breast cancer increases with age and because women age during a trial, it has been suggested that some of the delayed benefit of screening is due

to cancers detected through screening when women reach their 50s and menopause. Three trials reviewed at the conference found that about a third of cancers among women in their 40s were detected after the women turned 50. The British National Health Service (NHS) breast screening program conducted in the UK in 1997 avoids this "age-creep" problem by entering women at ages 40 and 41 and screening for five years, thus ensuring that all cancers are detected during the 40s. Important adverse effects reviewed at the conference included false negative and false positive mammograms and possible overdiagnosis because of ductal carcinoma in situ (DCIS), a precancerous lesion. All these problems were more frequent in younger women: screening misses up to a quarter of cancers in younger women (compared with a tenth in older women), and the false positive rate is higher in younger women, leading to more benign biopsies, increased costs, and greater anxiety. The percentage of mammograms read as abnormal (and the resultant percentage of false positive mammograms) varies by country. In the United States, about 11% of mammograms are read as abnormal, compared with fewer than 5% in the Scotland and Sweden trials. Proponents of screening suggest that technical improvements in mammography should mitigate the problems of false negative and false positive results. As I write these words, emerging news about computer-aided screening mammography is forthcoming. The early results are not very promising: they indicate that computer-aided detection is associated with reduced accuracy of interpretation of screening mammograms. The increased rate of biopsy with the use of computer-aided detection is not clearly associated with improved detection of invasive breast cancer.

Public health authorities should not advocate screening of unproved value. Some argue for giving information to people considering screening even when the only information available is complete uncertainty. Supporting the claim that patients could decide for themselves is preposterous. How can we expect patients to decide if the leading medical investigators cannot?

Aiming to resolve the controversy about the benefits of mammography as a screening modality for breast cancer in female patients age 40–49 years, a Clinical Practice Guideline published by in April 2007 in the Annals of Internal Medicine cited several recommendations that we shall go over seriatim.

Recommendation 1:
In women 40 to 49 years of age, clinicians should periodically perform individualized assessment of risk for breast cancer to help guide decisions about screening mammography.

A careful assessment of a woman's risk for breast cancer is important. The 5-year breast cancer risk can vary from 0.4% for a woman age 40 years with no risk factors to 6 % for a woman age 49 years with several risk factors. Factors that increase the risk for breast cancer include older age, family history of breast cancer, older age at the time of first birth, younger age at menarche, and history of breast biopsy. Women 40 to 49 years of age who have any of the following risk factors have a higher risk for breast cancer than the average 50-year-old woman: 2 first-degree relatives with breast cancer; 2 previous breast biopsies; 1 first-degree relative with breast cancer and 1 previous breast biopsy; previous diagnosis of breast cancer, ductal carcinoma in situ (DCIS), or atypical hyperplasia; previous chest irradiation; or *BRCA1* or *BRCA2* mutation. A family history can also help identify women who may have *BRCA* mutations that place them at substantially higher risk for breast and other types of cancer. These women should be referred for counseling and recommendations specific to this population, as recommended by the U.S. Preventive Services Task Force (USPSTF).

Recommendation 2:
Clinicians should inform women 40 to 49 years of age about the potential benefits and harms of screening mammography.

Screening mammography for women 40 to 49 years of age is associated with both benefits and potential harms. The most important benefit of screening mammography every 1 to 2 years in women 40 to 49 years of age is a potential decrease in breast cancer mortality.

A recent meta-analysis estimated the relative reduction in the breast cancer mortality rate to be 15% after 14 years of follow-up. An additional large randomized clinical trial of screening mammography in women 40 to 49 years of age found a similar decrease in the risk for death due to breast cancer, although the decrease did not reach statistical significance. Potential risks of mammography include false-positive results, diagnosis and treatment for cancer that would not have become clinically evident during the patient's lifetime, radiation exposure, false reassurance, and procedure-associated pain. False-positive mammography can lead to increased anxiety and to feelings of increased susceptibility to breast cancer, but most studies found that anxiety resolved quickly after the evaluation.

Recommendation 3:
For women 40 to 49 years of age, clinicians should base screening mammography decisions on benefits and harms of screening, as well as on a woman's preferences and breast cancer risk profile.

Because the evidence shows variation in risk for breast cancer and benefits and harms of screening mammography based on an individual woman's risk profile, a personalized screening strategy based on a discussion of the benefits and potential harms of screening and an understanding of a woman's preferences will help identify those who will most benefit from screening mammography. For many women, the potential reduction in breast cancer mortality rate associated with screening mammography will outweigh other considerations. For women who do not wish to discuss the screening decision, screening mammography every 1 to 2 years in women 40 to 49 years of age is reasonable. If a woman decides to forgo mammography, clinicians should readdress the decision to have screening every 1 to 2 years.

Recommendation 4:
We recommend further research on the net benefits and harms of breast cancer screening modalities for women 40 to 49 years of age.

There are few places in the developed world where a large scale trial could still be carried out to sort out these questions about breast cancer screening. As time goes on, questions remain about the usefulness of screening women in their 40s for breast cancer.

Colon cancer: Getting your rear in gear

Colon cancer is the second leading cause of cancer death in the general public, including in the elderly. Its prevalence in people 80 years and older is approximately 4%. Its incidence increases with age, is higher in African Americans than in whites, and is higher in men than in women. The overall incidence in people 85 years and older is 416 cases per 100,000, ranging from 393 per 100,000 in white women to 521 per 100,000 in African American men.

There are clear recommendations about when to begin colon cancer screening, but not about when to stop. Most clinical trials have focused on the benefit of screening in younger patients, and many trials excluded patients older than 70 years. Thus, clinicians have had to extrapolate the data for their older patients. In addition to the patient's age, we need to consider his or her functional status and comorbidities. The

risks and possible benefits of colonoscopy (relatively safe and considered the mother of all colorectal cancer screening tests) should be discussed with the patient, and his or her preferences should be taken seriously. The discussion below provides a framework for advising elderly patients about their individual benefit from colon cancer screening.

Most guidelines advocate some method of screening (flexible sigmoidoscopy, fecal occult blood testing, double-contrast barium enema or colonoscopy) in adults over the age of 50 years at average risk. Although definitive evidence is lacking (no randomized trials regarding colonoscopy have been published), most experts consider colonoscopy to be superior to other screening methods because, unlike flexible sigmoidoscopy, it allows one to view the entire colon, and unlike the noninvasive methods, it allows one to take biopsy specimens immediately. To determine the efficacy of a screening tool, the clinician needs to know the "number needed to treat" — or, in this case, the "number needed to screen" to benefit one patient. When this number is larger than the number needed for a complication to occur, the risk outweighs the benefit. For patients older than 75 years who have significant comorbidities and functional impairments that place them in the lowest quartile of life expectancy of their age group (discussed below), the risks of colonoscopy screening may outweigh the benefits.

Clinicians may try to individualize colon cancer screening by balancing the likelihood of finding polyps and the time for cancer transformation of a polyp against the patient's estimated remaining life expectancy. Given that few polyps transform into cancer in less than ten years, patients with a life expectancy less than seven to ten years may not benefit from detection and removal of precancerous polyps. The above discussion provides a framework for deciding whether an elderly patient should undergo colonoscopy screening. Important considerations are: If the patient has visible blood in the stools, colonoscopy ceases to act as a screening test but rather a diagnostic test. Colonoscopies performed in patients with symptoms are more likely to find colorectal disease than colonoscopies performed in patients without symptoms. If an older patient can tolerate the diagnostic procedure and is a candidate for intervention should disease be found, then colonoscopy should proceed.

More problematic, once again is all-cause mortality, which when considered, the benefits of screening disappear. An analysis of all-cause