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THE COURSE IS NOT ENTIRELY CLEAR

BY JENELLE PIFER

TO SCREEN OR NOT TO SCREEN

In this country and elsewhere, popular screening technologies for prostate cancer, breast cancer, and cardiovascular disease are being reevaluated. Do less-than-ideal findings prompt unnecessary worry for otherwise healthy patients? How do we know when a screening method helps more than it hurts? What if the up front costs outweigh the long-term savings? What can our society afford to do?

None of this is straightforward. Much is contentious. Most of us know someone who has been affected by one of these serious, and sometimes deadly, diseases. There is an awful lot at stake.

We recently heard from experts at the University of Pittsburgh who are helping patients and doctors navigate this treacherous territory. This panel of leading authorities—including Wendie Berg, an MD/PhD; Emma Barinas-Mitchell, a PhD; Steven Shapiro, an MD; and Joel Nelson, an MD—recently delved into these issues at "To Screen or Not To Screen," a presentation at this year's Pitt science festival, Science2012—Translation.

Proceed with caution.

In these excerpts from a discussion at the University's recent science festival, Pitt experts help us traverse the befuddling issues surrounding mammography, PSA testing, and cardiovascular disease screening (specifically, an imaging technology known as CIMT). Are the benefits of popular early detection methods outweighing the harm they do?

ILLUSTRATIONS | JESSE LENZ

The discussion also gave us a glimpse into how Pittsburghers are building a road to personalized medicine. This approach, many believe, could drastically change outcomes and help avoid pointlessly harmful (and did we mention costly?) testing, as well as treatment, down the line.

PROSTATE CANCER

"If you go looking for prostate cancer, you're going to find it," says Joel Nelson, an MD and the Frederic N. Schwentker Professor and chair of urology at Pitt, who coleads the University of Pittsburgh Cancer Institute's Comprehensive Prostate and Urologic Cancer Center, as well as its Prostate Cancer Program.

As far as cancers go, prostate cancer is pretty common: It accounts for nearly a third of all cancer diagnoses among American men. Nearly one in every four men harbors the disease, most after age 50; and one in six will be diagnosed. Though for most, having prostate cancer isn't necessarily a health problem. (More on that soon.)

The number of diagnoses has been increasing since the 1970s, says Nelson, but skyrocketed around 1994, when the prostate-specific antigen (PSA) test was approved by the FDA for asymptomatic men.

PSA is a protein produced specifically by the prostate that liquefies semen and helps sperm swim freely. It's found naturally in small quantities in the blood, but elevated levels are associated with prostate cancer, among other conditions.

The PSA test became the premier method for detecting prostate cancer in men without symptoms, but it's now beset with controversy: In general, the higher a man's PSA, the more likely it is he has prostate cancer. However, there is no specific "normal" amount of PSA in the blood, and fluctuations are often caused by benign factors, like having an enlarged prostate, recent ejaculation, and urinary tract infection. So, if a man receives a positive result, that really only leads to new questions and more screening—in the form of another PSA test to verify the numbers, or a biopsy.

In the end, at least two-thirds of men with elevated PSA levels do not have prostate cancer. It's easy to adopt a better-safe-than-sorry attitude, but the consequences of a false positive are not to be underestimated—including anxiety, stress, and the pain and side effects of biopsy, which involves inserting hollow needles into the prostate to remove tissue.

If two-thirds of men receive false positive test results, then it follows that the remaining one-third tested actually have the disease. Right? But even this could be considered "overdiagnosis," says Nelson. "Prostate cancer doesn't always behave in a malignant fashion," he says. Most of the time, it's indolent, meaning it's localized and might never progress to a clinically significant level over a lifetime. In fact, only about 16 percent of men diagnosed will develop metastases, Nelson says.

Unfortunately, the PSA test can't distinguish between the two forms of the disease, so doctors are presented with the challenge of figuring out which cancers are problematic.

With the PSA test, more men with the disease are finding out about it, and earlier. "There's been a real change in how men present with prostate cancer," says Nelson, noting that before the PSA test was standard, about half of men diagnosed had disease that was clinically localized. "A quarter . . . had metastatic prostate cancer, which is a lethal form of prostate cancer. Once the cancer leaves the prostate, there is no curative therapy for it.

"It's very different now: About 85 percent of the men we diagnose when they present have this clinically localized disease. Only 2 percent present with metastatic disease."

The metastatic group begins treatment, and the localized patient is left perplexed as to whether he should, too. Depending on how aggressive his cancer is, a man with localized disease can either: wait and watch for clinical symptoms, wait and continue testing ("active surveillance"), receive hormone treatment, undergo radiation (from an external beam or implanted seeds), or have his prostate removed. Side effects include erectile dysfunction, incontinence, and impotence.

"There's no question the treatments we apply are harmful. And this is a very expensive proposition if you assume that one man in six in the United States will be told that he has prostate cancer, and we have to do something about it in every case. It's going to bankrupt the country," says Nelson.

In February 2010, the American Cancer Society (ACS) advised that men with no symptoms who are expected to live at least another 10 years have a chance to make an informed decision about whether to get screened. PSA screenings would no longer be routine. There was great outrage, Nelson says. "Here's the cornerstone of cancer care in the United States telling us not to do what we think is a very important cancer test." Many physicians feel this early warning system, despite its flaws, is essential. "We're not talking about a disease here that's rare; we're talking about a disease that every 15 minutes somebody dies of," says Nelson.

Nevertheless, in May 2012, the U.S. Preventive Services Task Force, an independent group of national experts, echoed the ACS's conclusion when it recommended against using the PSA test for healthy men. It gave the procedure a "D" rating, meaning the task force had "moderate or high certainty" that the procedure is ineffective or that harms outweigh benefits.

Physicians nationwide are in a dilemma, says Nelson. "And if you remember your logic, a dilemma is being on the horns of something where you could go either way." On one hand, you use a less-than-ideal test to diagnose more men than you intend with a disease that may or may not be life threatening. On the other, what about the men really at risk of developing the lethal form of the disease? Isn't the test helping to reduce mortality?

A project known as the European Randomized Study of Screening for Prostate Cancer investigated this idea. It was conducted in eight countries throughout Europe from 1991 to 2003 and sought to answer the question, "If we screen for prostate cancer, can we reduce death from prostate cancer?" The study was vast: It included more than 180,000 men considered at risk for developing prostate cancer—that is, men ages 50 to 74. About half were screened regularly with the PSA test and half were not.

"If you go looking for prostate cancer, you're going to find it."

The results, published in *The New England Journal of Medicine*, indicated that about 16 percent of tests were positive. Of those patients, 80 percent received biopsies, of which a quarter had prostate cancer. "As you can see, if you go looking for prostate cancer, you're going to find it," Nelson repeats. That's about 6,000 cases of

prostate cancer and nearly double the diagnoses of the control arm.

The difference in mortality between the two groups, though, was minimal. The screened arm benefited by .71 lives saved per thousand. In other words, the study concluded that more than 1,400 men would need to be screened and 48 additional cases treated to prevent one death from prostate cancer. The conclusion was a little grim: Screening didn't do all that much to prevent prostate cancer deaths.

What's interesting, Nelson says, is what happened when the study updated its results in 2012 after an 11-year follow-up. The new number was 1.07 men saved per thousand. Nearly 500 fewer men needed to be screened to save one life. According to proscreening physicians, this speaks to the incremental benefit of the test.

"The longer you wait in a population that you've treated and intervened in, the better the results are going to be," says Nelson. Initially, the European study found 48 additional cases needed to be treated to save one life. In the follow-up it was down to 37. "If we waited another decade it would probably drop to 25. … The benefit is not in the first five years, it's [likely going to be] in the years 25 and 30 later." The idea, urologists feel, is that these curves will continue to widen. That is, the screening group will do better with time, and the control group is going to do worse.

The argument could also be made today, Nelson says, that reducing deaths from prostate cancer shouldn't be the only endpoint. Prostate cancer progresses slowly, rarely metastasizing to the vital organs, and many men with the lethal form die of unrelated causes. "It sits in your bones for about a year, a year and a half, painfully, before you actually die of the disease," says Nelson. "Really, we should think more about, 'What is the morbidity of the disease?' Because a lot of men who have metastatic prostate cancer may die of another cause, but they suffer from their prostate cancer."

Ultimately the recommendation of the ACS and the task force, Nelson says, has turned many patients away from screening. However, "it is still unfortunately true that the only effective therapy—and when I say effective, I mean curative therapy—is when you have localized disease. Once you have metastatic prostate cancer, the best we can do is delay progression. And although PSA is not at all specific for prostate cancer [it can be elevated for other reasons], it is actually quite sensitive. … It will clearly detect it when the cancer is localized and much more curable."

In upcoming years, Nelson fears, the move away from screening will likely mean a reversal of recent trends; growing numbers of men will present with disease that is metastatic and incurable.

What's more: Prostate cancer is a disease of the elderly. Screening typically doesn't even begin until a man is 50 years old; the median age of death from prostate cancer is 80. A huge segment of our population—the baby-boom generation—is approaching its most at-risk age. "There are going to be lots more much-older people around than there ever were in the history of mankind," says Nelson. "So we're caught: We see our population aging, and we have a test that doesn't work very well. How do we make [a solution] happen? Well, that's the challenge we face in our field."

For Nelson and many physicians, it's not whether to screen, but how to.

BREAST CANCER

Wendie Berg, an MD/PhD Pitt professor of radiology and an international leader in breast-imaging research, begins her Science2012 presentation with a claim that is simple and, some might say, pretty bold: "To some extent, mammography has been oversold."

To contextualize: Mammography is the best way overall to detect breast cancers when they're small and most treatable, and it's the only screening test proven to reduce death from the disease. It's still widely recommended for women age 40 and older, though there is some dispute over whether the test should be annual or biennial.

The newest controversy, however, lies in the increasing evidence that the test fails to detect many cancers in women with dense breast tissue. Of this population, more than 50 percent of women receive a false negative result.

"This is becoming a very hot topic right now," says Berg. In fact, a number of states, including Pennsylvania, are considering new legislation that would require doctors to inform patients when they have dense tissue, the dominant risk factor for a false negative after a mammogram.

Breast density is the proportion of glandular and fibrous connective versus fatty tissue present in the breasts. About half of all women in their 40s, and one-third of women older than 50, fall on the dense end of the spectrum and can be up to six times more likely to develop cancer. Unfortunately, dense tissue can also make it harder for doctors to spot problems on mammograms.

Consider this visual: On a black-and-white mammogram, tumors and their byproducts often appear as light masses on top of a darker backdrop. However, dense breast tissue, with cells bunched more closely together, brightens the entire scan, making it more difficult for doctors to distinguish between light and slightly lighter.

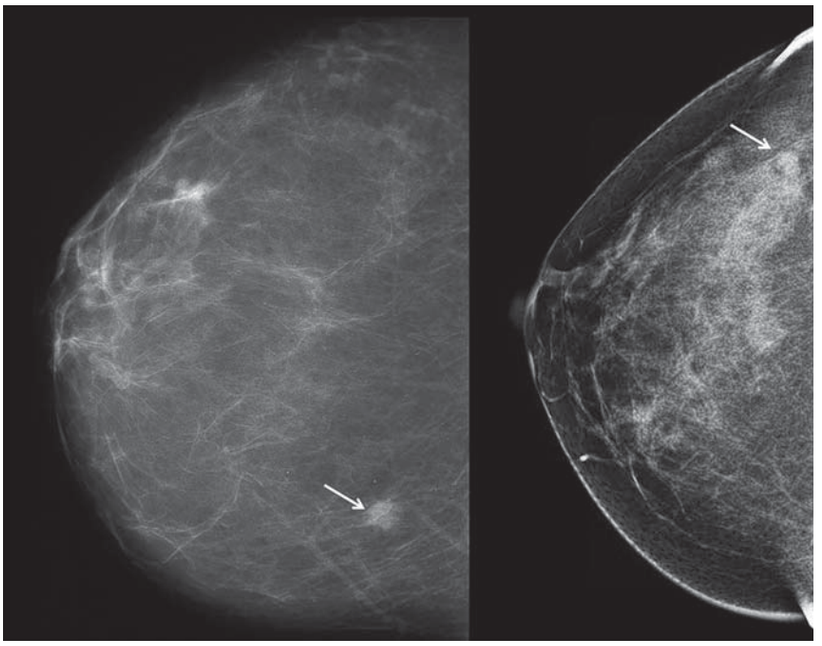
Traditionally, a radiologist would disclose tissue density on a mammogram report to the care provider by identifying the patient in one of four categories: almost entirely fatty, minimally scattered fibroglandular density, heterogeneously dense, or extremely dense. However, the new legislation would require a degree of increased transparency: Every mammography result letter given to a patient with dense breast tissue would have to inform the woman in plain language of her condition and note that she might consider asking her physician about the benefit of further testing. This legislation has already been passed in Texas, California, Virginia, New York, and Connecticut.

"Well, is additional testing a good idea?" says Berg. "This is a matter of some debate."

Often, additional testing comes in the form of an ultrasound or MRI (see "Lessons in Survival," Summer 2011), both of which are associated with a high rate of false positives. For example, of all the women biopsied after an ultrasound, only 10 percent have cancer. "That's a lot of unnecessary biopsies," says Berg. Essentially, we may run the risk of overcorrecting false negatives with false positives and subjecting healthy women to potentially harmful tests.

Nevertheless, in a study conducted at Pitt and Magee-Womens Hospital of UPMC and published in *Radiology* in March 2006, Marie Ganott, an MD assistant professor of radiology, determined that, of 1,500 patients in the breast-imaging suite, 86 percent were willing to go through the stress of recall and extra testing if it increased their chances of earlier detection.

"It is a very complex situation that we have in breast imaging, with a lot of opportunities," says Berg, who was recently recognized as a Medical Advancement Champion for Ground-Breaking Research Advances by the Avon Foundation and just won her second and third "Minnies"—Most Influential Radiology Researcher (2010 and 2012) and



COURTESY WENDIE BERG

In mammograms of two women with breast cancer, a tumor is easily visible in the patient with mostly fatty breasts (left). The patient with denser breast tissue (right) has cancer that is more difficult to detect. Comparing this image to prior mammograms helped her doctors detect the cancer.

Scientific Paper of the Year (2012)—from auntminnie.com.

"The only way I can wrap my hands around this is to at least propose that we are very strict about looking at the outcomes of women who are diagnosed with cancer and collecting information," about a patient's screening history, how the cancer was diagnosed, and her outcome, says Berg. "I think without this information, we're never going to be smarter."

The role of personalized medicine should also come into play when helping elderly women decide when to stop screening, Berg says. And that's a conversation that is often never held in this country. "It's very hard to tell someone not to get a mammogram. *What? They're not worth it anymore?*"

But the truth is, it typically takes nine years for the benefits of screening to be realized. "So, it really doesn't make a lot of sense, if a woman doesn't have at least a seven- to nine-year life expectancy, to push her to get screened," says Berg, because she's only going to experience the harms, not the benefits, of screening.

CARDIOVASCULAR DISEASE

When it comes to cardiovascular disease, the news is mixed. The bad part: It's the leading cause of death for both men and women and accounts for nearly one in three deaths in the United States. The good news: Deaths from the disease have been decreasing since the 1960s, largely because of improvements in how doctors focus on risk factors and better treatments.

Some of the most lethal iterations—coronary heart disease (number 1) and stroke (number 4)—have strong roots in atherosclerosis, a chronic process that begins early in life and truly lends itself to screening, says Emma Barinas-Mitchell, a PhD, assistant professor of epidemiology in Pitt's Graduate School of Public Health, and associate director of Pitt's Ultrasound Research Lab. "We can potentially detect individuals [who] are asymptomatic … and hopefully prevent events and death." But unfortunately, she says, "We don't have a perfect assessment."

Atherosclerosis is a chronic process wherein cholesterol and fatty substances accumulate in the arteries, harden into plaque, and disrupt blood flow. Screening is important, says Barinas-Mitchell, because, she explains, 40 to 60 percent of major atherosclerotic cardiovascular disease events show up seemingly out of the blue, as the first definitive sign of the disease. Atherosclerosis can remain asymptomatic for decades.

Typically, screening is performed by individually assessing established risk factors, like age, sex, cholesterol level, smoking status, and blood pressure, as part of a risk score, says Barinas-Mitchell. She cites the Framingham Risk Score, which predicts risk of cardiovascular disease over a 10-year period, as a widely used and valuable tool. However it has some drawbacks, she says. Namely, it hasn't proven to be accurate across all ages and ethnic populations.

So, wouldn't it be better if there were a way to physically see atherosclerosis and measure risk? That's the idea behind the carotid intima-media thickness test (CIMT), which uses ultrasound to measure the thickness of the inner layer (intima) and the second layer (media) of the carotid artery in the neck. This thickness represents a measure of atherosclerotic potential.

"The more risk factors you have, the thicker IMT you tend to have," says Barinas-Mitchell. "So, we know that [CIMT] predicts disease," Barinas-Mitchell says, but is it a better predictor than other methods, like the Framingham Risk Score? The answer, in short, is no.

Recent studies have cast doubt over the effectiveness of the test: CIMT was not associated with a reduction in cardiovascular events, and some studies proved it was a poor predictor compared to coronary artery calcification scores, which directly measure the calcification in the coronary arteries.

CIMT may have some incremental value. There is evidence the test is useful for patients considered at intermediate risk for developing heart disease, says Barinas-Mitchell. But that doesn't mean it is effective for widespread clinical use. "In terms of making global recommendations, I don't think we're there yet," she says. "Although, I think we can continue to use CIMT as a valuable research tool for understanding how and why atherosclerosis develops."

WHAT EXIT?

Is there a better way to approach early detection? What's ahead?

Perhaps the most fundamental way to think about the future of medicine is to remember we're all just a combination of genes and environment, says Steven Shapiro, professor of medicine at the University of Pittsburgh, as well as executive vice president and chief medical and scientific officer for UPMC and president of its Physician Services Division.

Genes and environment: These are two big columns with a million tiny variables that, when acting together, could spark a chain reaction toward a pathology. A predisposition for



Increasing evidence tells us that for women with dense breast tissue, mammograms fail to detect some noncalcified masses resulting from cancer and lead to an unacceptable number of false negatives. In these cases, supplemental screening with ultrasound can detect more cancers, but at the risk of more false positives.

developing lung cancer, for instance, adds up with the number of packs smoked on the front stoop. Poor diet and lack of exercise collude with family history of cardiovascular disease.

These are well-known examples of risk factors, but how we end up ill or healthy is not at all straightforward. So, amid a cacophony of cofactors, how can doctors efficiently assess what's wrong and how to fix it?

Historically and still today, doctors measure our health based on "a constellation of symptoms," like results of physical exams and laboratory tests, says Shapiro. "And to simplify things, we put them in categories." Doctors lump similar clinical presentations together and diagnose the problem, for instance, as diabetes or another chronic complex disease. "But these really are syndromes with multiple discrete molecular pathways, and because of that, patients have different manifestations of their disease."

With personalized medicine, rather, the emphasis is on using new methods of molecular analysis to understand the nuances of a person's genetic profile and optimize care with more precise diagnoses and targeted treatments.

The idea is that by studying molecular-level goings-on and environment, rather than symptoms, doctors can more precisely place patients into subpopulations and understand who is more likely to contract disease and how to prevent it. The foundation of personalized medicine, it is said, rests at the intersection of big data and big science. Or, put another way: First you have to know what you know, and then you can figure out how to use it.

In October, UPMC announced its commitment to fostering personalized medicine through big data. It launched a five-year, $100 million initiative to create a data warehouse that brings together clinical, financial, genomic, and other information that today is difficult to integrate and analyze.

Will there be growing pains associated with a personalized approach to care, as there are with today's early detection technologies? Perhaps. Yet, notes Shapiro, "The challenge that we have is greater than just taking care of patients, it's taking care of patients in a better way and saving the health of our economy." ■