DMS's Ann Gormley, M.D., chairs the Urinary Incontinence Treatment Network, a nine-site research group funded by the National Institute of Diabetes and Digestive and Kidney Disease.

A million overdiagnosed—and counting

Since the late 1980s, for every one man helped by the PSA (prostate-specific antigen) test, about 20 men have been unnecessarily diagnosed and treated for prostate cancer. And that's an optimistic estimate. The real ratio is probably closer to 50 to 1. These are some of the conclusions of a recent study conducted by DMS's H. Gilbert Welch, M.D., and Peter Albertson, M.D., a urologist at the University of Connecticut.

Rates: Welch and Albertson analyzed national data on age-specific prostate cancer incidence and death rates between 1986 and 2005. They estimated that about one million additional men have been diagnosed with and treated for prostate cancer since the late 1980s as a result of the PSA test. Then they looked at how many of those men likely benefited from being diagnosed, and how many exposed themselves to potentially dangerous treatments, in the form of radiation and surgery, with no benefit to their life span or quality of life.

"Approximately 56,500 prostate cancer deaths have been averted" since 1986, Welch and Albertson calculated. Under the "most optimistic assumption about the benefit of screening—that the entire decline . . . is attributable to this additional diagnosis—we estimated that, for each man who experienced the presumed benefit, more than 20 had to be diagnosed," they wrote in the *Journal of the National Cancer Institute*. And they say a more likely estimate—assuming that some of the improvement in prostate cancer mortality is a result of better therapies—is that at least 50 men had to be diagnosed for each prostate cancer death avoided.

"Many men who thought their lives were saved by being screened, diagnosed, and treated for localized prostate cancer are perplexed to learn that so few benefit," wrote Otis Brawley, M.D., chief medical officer of the American Cancer Society, in an editorial that accompanied the paper. The fact that the PSA test leads to overdiagnosis "is not a new finding," he continued. "What is new is the fact that many health professionals are finally accepting it as true."

"Many men . . . are perplexed to learn that so few benefit."

Of course there's no way to know, on an individual level, which men benefited from PSA screening and which didn't. Once a person has been treated for cancer, especially a small, slow-growing cancer, it's impossible to know if that cancer would have progressed into a deadly form if it had been left alone. And since few people are comfortable simply watching and waiting once they're told they have cancer, most diagnoses lead to treatment.

Predict: "We desperately need the ability to predict which patient has a localized cancer that is going to metastasize and cause suffering and death," Brawley wrote, "and which patient has a cancer that is destined to stay in the patient's prostate for the remainder of his life."

In many ways the PSA test is a gamble for most men: Will I be the one helped? Or will I be one of the 20 to 50 who is unnecessarily diagnosed and treated? For now, no one knows. JENNIFER DURGIN

JON GILBERT FOX

Welch and a collaborator looked at PSA's effects.

Viewer beware

Most of the 220,000 men diagnosed with prostate cancer each year look for information about the condition online. But, according to DHMC surgeon Peter Steinberg, M.D., what they find might not be very balanced. Steinberg and other researchers studied YouTube videos that discuss treatments for prostate cancer and the controversial prostate-specific antigen (PSA) test. They found that 69% of the videos expressed a bias in favor of screening or treatment, but none expressed a bias for less aggressive approaches. "YouTube is not a reliable source of information for individual patients seeking to better understand the screening for, and management of, prostate cancer," Steinberg wrote in *Urology*.

Doctor disparities

"We need to create incentives for surgeons to practice in rural areas," explained DMS surgeon Ian Paquette, M.D., at a recent gathering of the American College of Surgeons. Paquette made the suggestion in the context of presenting research showing that people living in the country are more likely to suffer a perforated appendix than are people living in the city. One reason for the regional difference, according to Paquette, is that there are more general surgeons in urban than rural areas.

At the International Conference on Alzheimer's and Parkinson's Diseases, DMS's Tracie Caller, M.D., made a presentation about selecting the optimal site of deep brain stimulation to treat Parkinson's.

Researcher builds a better microarray

Why do muscle cells contract, or neurons transmit signals, or cancer cells grow out of control? Every cell in a body has the same DNA, but which genes are turned on and which are turned off determines how a given cell acts.

Genes: The way scientists study gene expression has been revolutionized by a technique called a microarray. It used to be that only a few genes in a cell could be studied at once, but for the past few decades microarrays have allowed scientists to look at the behavior of tens of thousands of genes at once. Now, Dartmouth cancer researcher Craig Tomlinson, Ph.D., may have come up with a better way to do microarrays.

How a cell acts is controlled by the proteins it produces. Genes that are turned on send messages called RNAs that the cell then uses to make proteins. So scientists can tell from RNAs which genes are turned on. Microarrays let scientists look at the levels of virtually all RNAs in a cell on one small chip. "So one can essentially look at what a cell is producing to be that kind of cell," says Tomlinson.

Not all RNAs end up being made into protein, however. RNAs are made in a cell's nucleus and then move to the cytoplasm, where they are translated into protein. But, says Tomlinson, only about 5% of RNAs actually make it to the cytoplasm to become protein. Nevertheless, scientists have always done microarrays on all the RNAs in a cell, assuming the nuclear RNA wouldn't affect the results. Recently, Tomlinson posed a simple yet never-before-asked question: "Does the nuclear RNA matter?"

Their findings show that results using total RNA are very different.

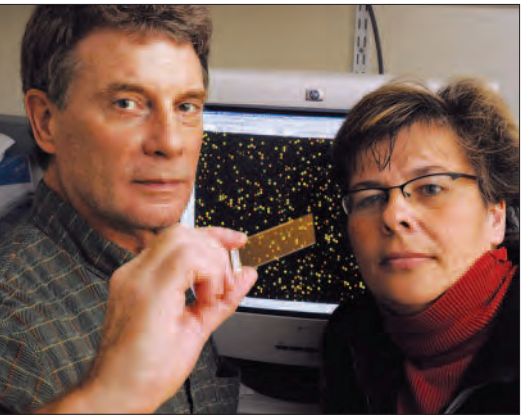
He and colleagues found it matters quite a bit. Their findings, published in the journal *RNA*, show that results using total RNA are very different from those using just cytoplasmic RNA. The difference is so profound, he believes it is imperative to get rid of nuclear RNA.

Test: Cancer researchers, explains Tomlinson, study "the different message RNAs made in a cancer cell versus a normal cell." Sometimes they find genes that, according to the microarray, appear to be expressed at different levels in a cancer cell than a normal cell—but further studies show there really isn't a significant difference. Tomlinson thinks many of these false positives may be caused by nuclear RNA. So if they test only cytoplasmic RNA, scientists may not have to chase after as many false positives.

The process of looking for a few differences out of many, many possible genes is sometimes referred to among scientists as "fishing." So, says Tomlinson, by including nuclear RNA in microarrays, "we've been fishing in the wrong pond."

But he's not stopping there. He thinks microarray results can be made better still by using RNA from just the polysome, the actual machinery in the cytoplasm that makes protein. So if his recent finding directed scientists to the right pond, his next one may show them what part of the pond to look in.

KRISTEN GARNER



JON GILBERT FOX

Tomlinson, left, and his lab manager, Heidi Trask, examine the RNA levels on a microarray chip.

Bubble trouble

Exercising right before undergoing a rapid change in air pressure may raise the risk of acquiring decompression sickness. Exercise causes tiny bubbles called micronuclei to form, but they had never been conclusively detected—until recently. DMS researchers had subjects exercise strenuously for 30 minutes. They then used a form of ultrasound to spot bubbles in subjects' legs. "The ability to measure micronuclei could offer a way to examine how and where they form, and their relationship to decompression sickness risk," they wrote in the *Journal of Applied Physiology*.

Benefits of breast-feeding

A team of DMS and DHMC researchers have made an intriguing finding with regard to breast-feeding and ovarian cancer. They studied hundreds of women with and without ovarian cancer and concluded that breast-feeding offers some protection against ovarian cancer—but only if the woman breast-fed her youngest child. There was no protective effect if a woman breast-fed some of her children but not her final child. "These findings," the authors wrote in the journal *Cancer Causes Control*, "which require confirmation by future studies, imply that breast-feeding resets pregnancy-related states that mediate ovarian cancer risk."

For a WEB EXTRA with a link to the video about testing well water, see dartmed.dartmouth.edu/w09/we06.

Dartmouth's Norris Cotton Cancer Center ranked among the top 5% of institutions nationwide in total research dollars from the National Cancer Institute in FY09—earning over $34 million.

Arsenic might be a factor in H1N1 severity

Arsenic in drinking water is a long-established cause of lung cancer. Until recently, however, there was suspicion, but little or no scientific evidence, that arsenic can promote nonmalignant lung disease. A lab at Dartmouth is helping to rectify the lack of evidence.

Chile: The Dartmouth researchers' interest was piqued by a 2006 study of a Chilean city, Antofagasta, that had a drinking water supply high in arsenic. Investigators in Chile and California compared its death records to those for the rest of Chile and found significantly higher death rates in Antofagasta due not only to lung cancer but also to inflammatory and obstructive bronchial disease.

The mice in the control group regained weight much more quickly.

After reading the 2006 paper, Courtney Kozul, a DMS graduate student in experimental and molecular medicine, collaborated with two DMS immunologists—Richard Enelow, M.D., and Kenneth Ely, Ph.D.—to test the finding.

Kozul conducted the study using three groups of mice. One group got drinking water containing 100 parts per billion (ppb) of arsenic. A second group got water with 10 ppb of arsenic—the current Environmental Protection Agency maximum for arsenic in drinking water—and a control group got water with no arsenic.

JOSEPH MEHLING

Kozul showed that arsenic can affect immunity.

At the end of five weeks, the lungs from all the mice were removed and analyzed by a process called whole genome transcriptome profiling, in which the RNA products of each mouse's genome—40,000 RNA transcripts—were identified using a microarray. The resulting data was then crunched by a computer to see which RNAs increased with exposure to arsenic and which decreased.

Kozul was struck by the fact that many of the RNAs that decreased are known to be associated with genes that are important regulators of innate immunity. This was a significant finding in and of itself, but Kozul and her colleagues wanted to know more. "We were interested to know if there was a functional consequence of these changes in gene expression," says Kozul. In other words, would the changes affect immunity in a live mouse?

Flu: So the arsenic-exposure part of the experiment was repeated, this time with two groups of mice—one that got 100 ppb and one that got none. This time, at the end of the five-week period the mice were infected with H1N1 flu virus. The researchers then observed how quickly the mice recovered from the flu, using weight gain as a measure. The results were clear-cut. All the mice lost weight as a result of the flu, but the animals in the control group regained it much more quickly than those exposed to arsenic—strongly suggesting that arsenic exposure results in compromised immune function.

Kozul notes that in New Hampshire, municipal water supplies are regularly tested for arsenic, but testing of private wells is up to homeowners. To help homeowners, some of Kozul's colleagues recently produced a video about how to have well water tested. ROGER P. SMITH, Ph.D.

Octogenarian outcomes

The number of U.S. octogenarians is predicted to double between 2000 and 2050. Many people in this demographic eventually develop heart disease, raising the question of whether the benefits of surgery to treat it outweigh the age-related risks. In a large study, Donald Likosky, Ph.D., and colleagues found that patients over 80 who underwent aortic valve surgery did, on average, benefit, with over half surviving more than six years. "This study presents the largest experience to date of octogenarians undergoing surgical treatment of aortic stenosis," the authors wrote in *Circulation*.

Counting all costs

According to DMS researchers, changes in surgical technologies may have hidden costs. They compared open colectomies—an older approach—to laparoscopic colectomies—a newer, minimally invasive technique. There is little difference in the dollar cost of performing the two procedures, but the laparoscopic approach takes about 27 minutes longer. The lost time, say the researchers, adds up to between $240 and $700 more in opportunity cost per procedure. "Although frequently overlooked, opportunity cost is a potentially very important element in assessing the true costs of surgical innovation," they wrote in *Surgical Endoscopy*. ■