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HEALTH JOURNAL

The Prostate Cancer Quandary

By MELINDA BECK

Scientists may soon be able to answer the agonizing question facing men with prostate cancer: Does their cancer need immediate treatment or can it be left alone?

Some 218,000 American men will be diagnosed with prostate cancer this year. An estimated 85% of those tumors will grow so slowly that they will never cause problems. But the rest are aggressive and lethal. As of now, there's no way to tell early on which cancers are which, so tens of thousands of men undergo surgery or radiation each year for cancers that never needed treatment, risking impotence or incontinence in the process.

Several recent genetic discoveries could help doctors evaluate how aggressive a man's prostate cancer is much earlier. Scientists at the University of Michigan have identified at least 24 different kinds of prostate cancer of varying virulence whose DNA signatures can be read like a bar code. Memorial Sloan-Kettering Cancer Center researchers have identified other genetic subtypes of prostate cancer that seem to predict whether the tumor will be low or high risk. And Harvard Medical School scientists have found a specific gene that causes prostate cancers to spread. Some of the discoveries also could lead to new treatments, tailored specifically for the kind of prostate tumor a man has.

Such genetic tests for prostate cancers would go well beyond the current PSA test (for prostate-specific antigen) used for screening men in general. PSA tests have helped find prostate cancers at much earlier stages, saving thousands of lives in recent years. But PSA levels also rise for reasons that have nothing

to do with cancer, prompting many men to have prostate biopsies each year that don't find cancer or that find tumors of the slow-growing variety.

Scientists say new prostate-cancer tests could be available in the not-too-distant future. "It won't be tomorrow, but if you go by the pace at which such technology entered the field of breast cancer, it will be several years [for new prostate tests], not a decade," says Charles Sawyers, chairman of human oncology and pathogenesis at Memorial Sloan-Kettering.

At the University of Michigan, researchers have focused mainly on what are known as gene fusions, in which DNA from some genes gets stuck to other genes, altering what they do. Two of the 24 types they have identified involve the same gene, known as RAF, that drives malignant melanoma, according to a report in the journal *Nature Medicine* this month. Although those two types make up only about 2% of the tumors studied so far, they are highly aggressive, killing an estimated 3,600 men each year.

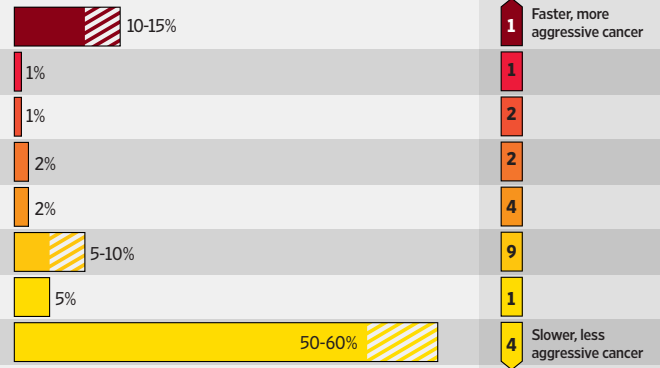
Treatment for those prostate cancers is on the horizon. Several anti-RAF drugs to treat melanoma have regulatory approval or are in late-stage clinical trials. Early lab tests show that some of those drugs are effective against RAF prostate-cancer cells.

Most of the remaining prostate-cancer types involve fusions of a gene called ETS, and they are more or less virulent depending on which fragments of other genes are fused to them. Jonathan Simons, chief executive officer of the Prostate Cancer Foundation, which funds much of the Michigan research, likens the process to rebuilding car engines out of random automotive parts.

How Aggressive Is That Tumor?

Researchers at the University of Michigan have identified 24 types of prostate cancer with varying degrees of virulence.

PERCENTAGE OF TOTAL PROSTATE-CANCER CASES



Source: Michigan Center for Translational Pathology, University of Michigan

"If you have a tumor with a lawn-mower engine, it may look like a cancer, but it may never be a problem in the life of a 72-year old man," he says. "But if you have a cancer with a bulky Dodge Hemi stuck to a BMW 850csi V-12 engine, that needs treatment."

Four of the 24 cancer types discovered, which together make up over 50% of the prostate cancers classified so far, have the equivalent of lawn-mower engines and probably don't have enough power to grow past the prostate gland, Dr. Simons says. Another 20% are more highly powered and could pose problems in the presence of other gene fusions.

Getting Aggressive

And one of the most aggressive types, representing 10% to 15% of prostate cancers, appears to follow a different mechanism: It results when there are excess amounts of a protein known as SPINK1. Since the protein shows up in urine, the researchers say

a urine test could be designed to measure its presence.

There could be more types, represented by different genetic bar codes. "We are finding more every month or so, filling in the gaps," says the lead investigator Arul Chinnaiyan, director of the Michigan Center for Translational Pathology. To validate the findings, researchers, who so far have studied some 300 tumor samples, plan to analyze at least 1,000 samples and to follow how the patients progress.

"We are not there yet, but within the next year, we hope to have a clinical lab test where we can predict what kind of cancer a man has," says Dr. Chinnaiyan.

Researchers at Memorial Sloan-Kettering are studying a different kind of genetic error involved in prostate cancer. Instead of two copies of a gene, some cancer cells have too many or too few, known as copy-number alterations.

In a study in the journal *Cancer Cell* last week, the researchers analyzed the copy-number alterations in 218

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DOWJONES

Prostate cancer cell

Chromosome

Genes

Note: Illustrations are schematic.

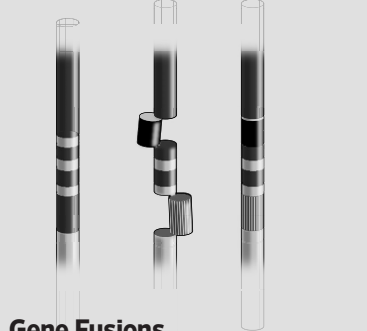
Finding

Goal

Researchers

What the Genes Tell

Researchers are closing in on ways to determine whether a prostate tumor is likely to metastasize, based on gene analyses.

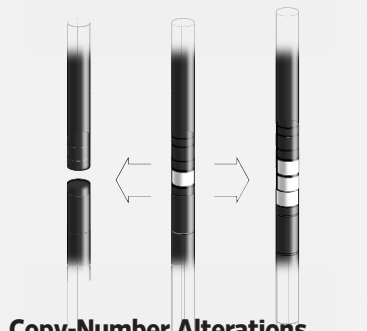


Gene Fusions

At least 23 types of prostate cancers occur when fragments of genes break off and fuse to others. Two of the most aggressive types involve the same gene (RAF) that drives malignant melanoma. One other type involves too much of a protein called SPINK1.

Tests reading the genetic bar code of biopsy samples—or tumor metabolites in urine—could **predict tumor aggressiveness and target drug therapies**; RAF tumors may respond to melanoma drugs.

University of Michigan

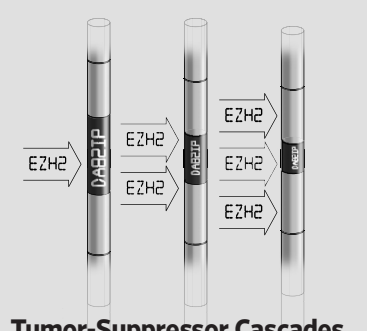


Copy-Number Alterations

Prostate cancers may contain too many or too few copies of some genes; the more copy-number alterations (CNAs), the more aggressive the tumor.

Tests measuring CNAs in biopsy samples could **predict which tumors represent low and high-risk** disease.

Memorial Sloan-Kettering Cancer Center



Tumor-Suppressor Cascades

When prostate cells have too much of an enzyme called EZH2, it suppresses a gene called DAB2IP, which normally acts as a brake for cancer. The more EZH2, and the less DAB2IP, the more likely a tumor will metastasize.

Tests measuring EZH2 and DAB2IP in biopsy samples could **predict aggressiveness and suggest treatments** using EZH2 inhibitors.

Brigham and Women's Hospital; University of Michigan; University of Texas Southwestern Medical Center

cancerous prostates surgically removed at Sloan-Kettering and found that they fell into six clusters. Those clusters corresponded closely with how quickly the patients' cancer returned, judging by their PSA.

"It was a surprise to us that so much prognostic information was there in the original samples after surgery," Dr. Sawyers says. Ideally, "we'd be able to tell a man, 'Your tumor looks like it's in cluster five, so you should get surgery and radiation and perhaps even more aggressive therapy. Or, you are in cluster two, so you can relax and maybe just get another biopsy in another year and see if your cluster has changed,'" he says.

Tracking Patients

Further testing at Sloan Kettering is continuing. The researchers have 1,000 additional samples from prostates removed more than 10 years ago and can correlate their findings with how the patients fared in that time.

In still another recent breakthrough, researchers at Harvard Medical School identified a gene pathway directly involved in prostate-cancer metastasis. They isolated a gene, DAB2IP, that acts as a brake for cancer.

When too much of an enzyme, EZH2, is present, the DAB2IP gene is suppressed, removing the brake and allowing the cancer to spread.

"It's more than just correlation; it's cause and effect," says lead researcher Karen Cichowski, a cancer biologist, who demonstrated the process in mice in a study in *Nature Medicine* this year. The Harvard researchers also studied data from human prostate cancers and found that the patients with the most aggressive tumors had either excess EZH2 or too little DAB2IP or both.

These findings, too, could yield tests to predict how aggressive a patient's prostate cancer could be. Several biotech companies have drugs in the works to inhibit EZH2.

The various research findings complement each other by describing different ways that genes mutate as cancers evolve, says Dr. Chinnaiyan. He expects that diagnostic tests in the future will look at a variety of genes, as well as proteins, molecules and other "biomarkers" to predict how aggressive a cancer might be.

Another technique being applied to prostate cancer

involves magnetic resonance spectroscopy, a form of imaging that tracks chemical changes in tissues. In a small study in the journal *Science Translational Medicine* this year, researchers at Harvard showed that the scanning technology can not only locate cancers within the prostate, but also has the potential to distinguish fast and slow-moving cancers.

Progress is also being made on ways to measure prostate cancers through simple blood and urine tests, or what scientists call "liquid biopsies." The biotech firm Gen-Probe Inc., working with the University of Michigan researchers, has developed a test for a gene called PCA3 that shows up in urine only when a man has prostate cancer.

For now, the PCA3 test is mainly useful to tell men who have a rising PSA level that they should have a biopsy as well, or for men who have a negative biopsy that might have missed cancer. Dr. Chinnaiyan hopes the PCA3 test can also check for gene fusions that can identify which type of prostate cancer a man has.

'Liquid Biopsies'

The PCA3 test is not yet

approved by the Food and Drug Administration, but it is approved for use in Europe and is available in several U.S. labs on an investigational basis.

In other prostate-cancer news, there's more evidence that cholesterol-lowering statin drugs may play a role in controlling the spread of prostate cancer. In a study in the journal *Cancer*, researchers at Duke University Medical Center and elsewhere analyzed the records of 1,319 men who had their prostates removed between 1988 and 2008 and found that 304 of them had a rising PSA level after surgery, which generally indicates that the cancer has reoccurred and spread. Men who were taking the equivalent of 20 mg of simvastatin a day were 43% less likely to see a recurrence. In men taking a higher dose, the risk of recurrence was reduced by 50%.

The researchers cautioned that the reduced risk could be due to factors other than statins, such as diet, exercise or smoking habits; only a randomized clinical trial could tell for sure. Five other recent studies also have found that statins appear to lower the risk for advanced prostate cancer.