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Keeping Vigilant

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Bladder cancer has the highest risk of recurrence of all cancers, ranging from 50 to 90 percent depending on stage, grade and number of tumors. And because of this risk, follow-up and subsequent therapy over a survivor's lifetime also makes bladder cancer the most expensive cancer, costing up to \$187,000 based on research published in *Pharmacoeconomics*. Because such a high percentage of bladder cancer patients may develop a recurrence, monitoring is crucial.

Several urine tests are currently approved by the Food and Drug Administration for detecting early bladder cancer or for monitoring for recurrence. NMP22 BladderChek, approved in 2005, uses technology similar to that found in over-the-counter home pregnancy tests. Other diagnostic tests include UroVysion, which measures chromosomal abnormalities with fluorescent in situ hybridization (FISH), and ImmunoCyt, which looks for abnormal proteins on the surface of the same cells collected for urine cytology.

The problem with these tests is their reduced ability to find recurrent tumors, partly because new tumors discovered during active surveillance tend to be much smaller than those that first bring patients to the urologist's office. No single test is very reliable in detecting cancer alone and more than half of cases result in false positives, meaning more anxiety, tests and costs before cancer can be ruled out. "With the FISH test, for instance, if you get a positive result and you don't see a tumor, it doesn't necessarily mean the test is wrong," says Michael O'Donnell, MD. "Sometimes it can predict a tumor recurrence within the next year. And because of that, maybe we check a little more often, we're more vigilant and we do more tests looking at other places the abnormality may be coming from."

It is not clear whether any currently approved test is superior to another because there is always a trade-off between sensitivity and specificity. A high sensitivity misses fewer cancers, but increases false positives. On the other hand, high specificity reduces false positives, but more cancers may be missed.

Researchers are experimenting with monitoring microsatellite instability—DNA alterations that occur in cancer cells as they begin to proliferate. Another experimental test measures a substance called survivin, which helps prevent cancer cell death. Preliminary data also show that a test using mass spectrometry

(a method of measuring and analyzing protein fragments) has higher specificity and fewer false positives than other urine tests. The test looks for 22 biomarkers for bladder cancer, including an overabundance of a key protein called fibrinopeptide A, which has also been identified in ovarian and gastric cancers. Researchers are now planning studies with bladder cancer survivors that should help define the best method for predicting recurrent cancer.