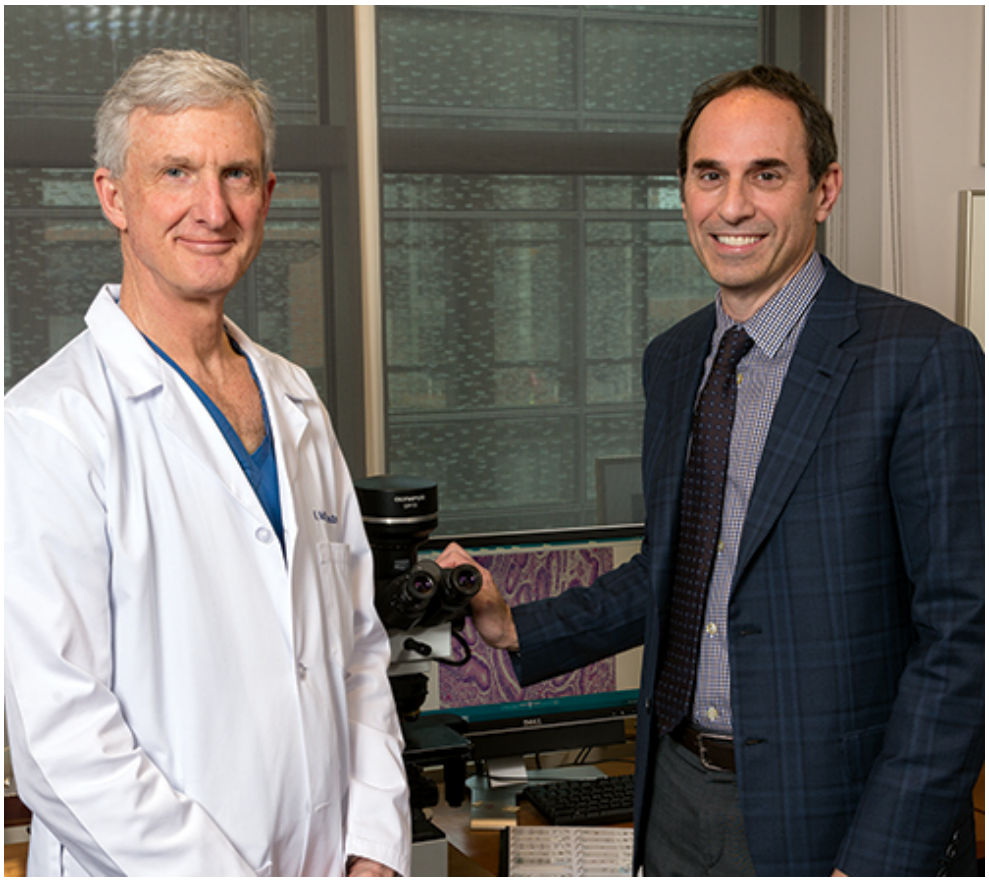
Keeping an active eye on prostate cancer

William Check, PhD

April 2015—In December 2011, M. Elizabeth H. Hammond, MD, was a member of an expert panel for an NIH State-of-the-Science conference on the role of active surveillance in managing men with localized prostate cancer. At these public meetings patients can address the panelists. “There was a lot of concern among patients and some of the panelists that pathologists were not doing everything we could to support the concept of active surveillance,” says Dr. Hammond, a professor of pathology at the University of Utah School of Medicine. “Patients perceived pathologists as not being engaged in the treatment dilemmas they faced.



Dr. Jonathan Epstein (right) and Dr. H. Ballentine Carter were two members of the group that wrote the consensus statement on the role of pathologists in determining eligibility for active surveillance. Dr. Epstein and others are also proposing a new five-level grading system.

“Our inability to communicate to patients and clinicians about our diagnostic process was causing them to discount the biopsy as a way to determine whether they should be on active surveillance. It was a horrible experience for me to see how badly we pathologists were perceived,” she recalls.

Active surveillance is an important strategy for men with low-grade disease. “And we are in a pivotal place as far as this treatment is concerned,” Dr. Hammond says. “Our role as pathologists is critical in helping to define which prostate cancer patients are eligible and to determine whether a patient should continue to be followed on active surveillance or whether his disease has progressed.”

Dr. Hammond shared her concerns with Mahul Amin, MD, professor, medical director, and chairman of pathology at

Cedars-Sinai Medical Center, who spearheaded an initiative by the CAP, other pathology organizations, and the Prostate Cancer Foundation to achieve consensus on the critical role of pathologists in determining eligibility for active surveillance.

“To bring greater credibility to the pivotal document and to reiterate that contemporary prostate cancer treatment is a team science,” Dr. Amin says, “it was important to assemble a multidisciplinary international team of pathologists, urologists, radiation oncologists, and scientists to coauthor this consensus paper.” Face-to-face meetings, numerous conference calls, and “passionate discussions through emails and personal communications” is what led up to its creation, he says.

Dr. Hammond adds, “The College has done everything it can to support the consensus statement, including provide financial support.”

Dr. Amin

The consensus statement was published last fall (Amin MB, et al. *Arch Pathol Lab Med.* 2014;138:1387–1405). “The goal of the document was to deal with aspects of diagnosis that were problematic and to give guidance to pathologists on how they could do a better job providing diagnostic information that would guide treatment options,” Dr. Hammond explains. One example: “The document talks about the definition of insignificant prostate cancer, which is only Gleason score six,” she says. “This should help a lot.”

To formulate the statement, a panel of primary pathologists, genitourinary pathologists, and urologists was assembled, one of whom was Lawrence True, MD, professor of pathology and chief of genitourinary pathology at the University of Washington. “It has become far more widely appreciated among all of us who deal with prostate cancer that there is overdiagnosis and consequent overtreatment,” Dr. True says. “To address this, we tried to get a consistent way of making the diagnosis and grading prostate cancers and characterizing other features that we think are associated with the behavior of the tumor, such as the amount of invasive cancer on needle biopsy.”

Consistent high-quality pathology is what is needed to increase the percentage of men on active surveillance, says Jonathan I. Epstein, MD, professor of pathology, urology, and oncology at Johns Hopkins School of Medicine, who was a member of the consensus panel. “Clinicians will trust pathologists more and rely more on our reports.”

“There is no question that certain well-known urologists in the U.S. do not support active surveillance,” Dr. Epstein says. Overall about 10 percent of men with prostate cancer who are eligible for active surveillance go on that regimen, compared with about 50 percent in Canada. A recently published study finds that about two-thirds of men newly diagnosed with prostate cancer are eligible for active surveillance (Overholser S, et al. *J Urol.* Epub ahead of print Jan. 27, 2015;doi: 10.1016/j.juro.2015.01.089). The authors concluded that “the majority of men in the US who are diagnosed with prostate cancer based on regular PSA testing are likely to be eligible for active surveillance and should be carefully counseled regarding the risk of their disease as well as the consequences of treatment.”

In addition to recommendations in the consensus statement, Dr. Epstein says, “We are proposing a new five-level grading system. In the near future it may replace the Gleason grade.” One of the problems with the current scoring system, he says, is that “it can instill fear in patients.

“If a patient is told he has a Gleason score of six, he may go to the Internet and see that six is in the middle of the scoring range. However, it is the lowest score you can get these days. Perhaps a revised scoring system would help alleviate some patient concerns,” Dr. Epstein says.

One of the urologists on the panel was H. Ballentine Carter, MD, professor of urology and oncology at Johns Hopkins. “Good pathology is vitally important” for active surveillance programs, says Dr. Carter, who worked with the subgroup that addressed clinical perspectives on active surveillance. Two randomized trials addressed this question, he says. “Both suggested that for men who are older—and older is a somewhat subjective term, most would agree age 55 or over—with favorable disease, active surveillance is a safe management option over at least 10 to 15 years. My own opinion is that a man over age 65 with favorable-risk disease ought to ask himself not which treatment he needs but whether he needs treatment.”

Dr. Humphrey

Panelist Peter A. Humphrey, MD, PhD, calls the consensus statement “a really important initiative by CAP and other pathology organizations” and “a strong response from our specialty speaking of the importance of what we do as far as getting patients into active surveillance.”

Dr. Humphrey, a professor of pathology and director of genitourinary pathology at Yale School of Medicine, was a member of the subgroup that addressed tumor quantification. “In our recommendations we listed factors related to how to quantify the amount of cancer,” he says. “We surveyed a wide variety of methods. A real strength of this paper is the summary in Table 5 of the variety of tumor extent measurements from the literature. We analyzed which are most powerful in predicting clinical outcomes.” (See “Tumor extent measurements,” page 42.)

In addition to traditional measures to qualify newly diagnosed patients for active surveillance, Dr. Humphrey and his colleagues are using a new imaging tool called multiparametric MRI with fusion of ultrasound images and biopsy. “Emerging data suggest this method better helps identify high-grade cancer,” he says.

Biomarkers are another possible adjunctive method for classifying tumor invasiveness. “I have been interested in molecular markers for several years,” E. David Crawford, MD, says. “I believe that if we had these biomarkers several years ago, we wouldn’t have had this backlash about overdiagnosis and overtreatment and repeat biopsy.” Dr. Crawford is a professor of surgery/urology/radiation oncology and head of urologic oncology at the University of Colorado School of Medicine. (See “Molecular markers to lessen the uncertainty,” page 46.)

Recommendations on quantifying cancer in biopsy cores are to report the number of cores submitted and the number of positive cores, Dr. Humphrey says. In addition, the recommendation is to always provide the linear percentage of cancer in the core that has the greatest amount of cancer. This last criterion is not so simple. Two methods are commonly used when a core contains foci of cancer separated by benign tissue—to sum only the cancer foci or to incorporate the benign stroma. It’s not clear which approach is more predictive. “We need more data with hard clinical endpoints,” Dr. Humphrey says.

Which method you use can be crucial. Many active surveillance programs exclude a patient who has more than 50 percent cancer in the core with the greatest amount of cancer. “So how you measure these foci could have a huge impact on whether the patient is eligible for active surveillance,” Dr. Humphrey says. The consensus recommendation strikes a compromise. One might report “two discrete foci involving 10% of the core but spanning 70% of the length.” Currently Dr. Humphrey incorporates benign stroma in his report, using the term “discontinuous involvement.”

At Johns Hopkins, Dr. Epstein says, “We only get the length of cancer from one end to the other. An increasing

number of studies show it is more accurate to include benign tissue in the estimate." What is most important is to make sure the clinician knows how you are measuring.

Even more important in determining eligibility for active surveillance than percent of cancer involvement in cores is Gleason grade. "Grade inflation" has complicated this measure since 2005, when the International Society of Urological Pathology (ISUP) reclassified prostate biopsy cores containing cribriform adenocarcinoma as high grade; now they are automatically Gleason pattern four.

Participant characteristics and inclusion criteria for several large active surveillance cohorts

				Inclusion Criteria				
Source, y	Patients, No.	Age, y	Nonwhite, %	Clinical Stage	PSA, ng/mL	Gleason Score	Prostate Biopsy[a]	Other Criteria
Lin et al,[152] 2013	351	63.8[b]	9	≤T2	≤10	≤7 (3+4)	≤33A	
Cooperberg et al,[31] 2011; and Glass et al,[52] 2012	640	62[c]	18	≤T2	≤10	≤6	≤33B, ≤50C	
Klotz et al,[30] 2010	453	70[c]	NR		≤15	≤7 (3+4)		
Selvadurai et al,[172] 2013	471	66[c]	NR	≤T2a	≤15	≤7 (3+4)	≤50B	
Adamy et al,[173] 2011	238	64[c]	NR	≤T2	≤10	≤6	≤3D, ≤50C	
Bul et al,[174] 2013	2494	65.8[c]	NR	≤T2	≤10	≤6	≤2D	PSAD ≤0.20
Patel et al,[175] 2014	870	66[c]	10	T1c		≤6	≤2D, ≤50C	PSAD ≤0.15

Abbreviations: NR, not reported; PSA, prostate-specific antigen; PSAD, prostate-specific antigen density. aBiopsy code: A, percentage of positive cores; B, percentage of cores; C, percentage of any core; D, No. of cores. bMean cMedian. In "Source" column, reference numbers are as listed in Arch Pathol Lab Med. 2014;138:1387–1405. Reproduced with permission.

"ISUP formally recommended what a lot of us had already been doing," Dr. Humphrey says. "This has created a pure category for Gleason pattern three, which is now a relatively indolent cancer with little to no chance of metastasis."

Dr. Humphrey cites a large study of more than 14,000 radical prostatectomies in which no patient with true Gleason score of six or less had lymph node metastasis (Ross HM, et al. *Am J Surg Pathol.* 2012;36:1346–1352). Conversely, a report early this year from the University of Toronto active surveillance program on 993 patients found that almost all patients with metastases had high-grade disease (Klotz L, et al. *J Clin Oncol.* 2015;33:272–277).

Dr. Epstein was in the subgroup that discussed Gleason grading. While Gleason described five patterns, Dr. Epstein notes that pattern one is virtually nonexistent. "In practice, six is the lowest score you get," he says. So although there are 25 possible scores (including permutations), most scores are not used. "There are five distinct grades," Dr. Epstein says. "That's why we have come up with a five-level grading system."

In the system Dr. Epstein and others are proposing, scores (3+3) or below are called Grade Group 1; (3+4) is Grade Group 2; (4+3) is Grade Group 3; Gleason score eight (by any permutation) is Grade Group 4; and Gleason scores nine and 10 are Grade Group 5. The new system separates the two types of Gleason score seven (3+4) from (4+3) because the latter has a more severe prognosis.

Support for the proposed new system comes from a retrospective review of more than 21,000 prostate cancer patients who had radical prostatectomy and 5,000 who had radiation therapy at five institutions—Hopkins, Cleveland Clinic, University of Pittsburgh, Memorial Sloan Kettering Cancer Center, and Karolinska Institute—as part of an ongoing trial. "We started with 2005 to make sure we had contemporary grading," Dr. Epstein says. The study was submitted recently for publication.

"In general, we found we can distill prostate cancer into five distinct grades for a simplified system that is accurate

and reflects disease better and is less worrisome for patients than the way grades are currently reported," he says.

Dr. Epstein calls men with Grade Group 1 (Gleason score six) cancers "excellent candidates" for active surveillance. "In addition, there may be some men with Grade Group 2—(3+4)—tumors who could also be candidates for active surveillance, depending on factors such as cancer extent on biopsy, percentage of pattern four, age, comorbidity, and patient preference. That will be an area of additional investigation in the future." Three of the seven major active surveillance programs listed in Table 1 of the consensus document include men with (3+4) prostate cancers; they will provide information on the prognosis of these patients. (See "Participant characteristics and inclusion criteria for several large active surveillance cohorts.")

Even with good classification parameters, active surveillance has risks. "With needle biopsy, about 20 percent of the time when a patient has a Gleason score of six, there may be higher-grade tissue present in the rest of the prostate," Dr. Epstein says, noting there will always be some sampling error. "That is why we repeat the biopsy every year, not so much for progression but in case we missed high-grade tissue on the initial biopsy."

Even so, active surveillance can never be 100 percent safe. "No matter how much we follow and re-biopsy, relatively rare patients on active surveillance will have bad disease and have potentially lost their window of curability," Dr. Epstein says. "Some urologists want it to be 100 percent safe. But that is not viable. There is a balance of benefit. Overtreating many men to save the exceptional patient does more harm than good."

Dr. Hammond

Dr. Hammond notes that the consensus document quantifies the risk of active surveillance. During radical prostatectomy, 35 percent of patients are found to have a higher Gleason score than at diagnosis. "However," she notes, "active surveillance is useful because men with prostate cancer are very unlikely to die of their disease." With surgery, the 20-year risk of prostate cancer-specific mortality for men with low-risk disease is 1.6 percent; among men on active surveillance, it is 2.8 percent. Curative treatment provides an average 1.8-month increase in life expectancy.

"The difference is not trivial," Dr. Hammond acknowledges. "However, 97 percent of men with Gleason score six on cancer will not die of it while on active surveillance."

In this context, Dr. Hammond says the consensus statement provides an important service by defining insignificant prostate cancer, "because that will not kill you." Prostate cancer must meet three criteria to be deemed insignificant: only Gleason score six histology, organ confined tumor, and volume

The good prognosis for carefully selected patients on active surveillance and the surgical and radiation treatment-associated morbidity are why "it's important that patients know they have another option besides radical prostatectomy or radiation therapy," Dr. Hammond notes. And that brings up another area where pathologists need to play a role: supporting shared decision-making between clinicians and patients, with "patient preference as a way of defining treatment.

"The goal of all the work being done in prostate cancer is to get the most accurate evidence and information to present to a patient, so when the patient meets with a clinician they can together come up with the best treatment plan, including how the patient feels about various therapeutic options," Dr. Hammond says. "Our information and

evidence must be as accurate as possible. If you throw uncertainty about the value of the pathology information into the mix, it will be much more difficult for that conversation to be useful."

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Tumor extent measurements

- Number of positive cores
- Fraction of positive cores
- Linear percentage × carcinoma in each site (core)
- Linear percentage carcinoma in core with the greatest amount of tumor
- Overall linear percentage of carcinoma across all sites (cores)
- Linear millimeters of carcinoma in each site (core)
- Linear millimeters of carcinoma in the core with greatest amount of tumor
- Total linear millimeters of carcinoma across all sites (cores)

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Several panel members discussed their institutions' active surveillance programs. In the program at Johns Hopkins, Dr. Epstein says, "a somewhat complicated algorithm" is used. Basically, repeat biopsy is done every one to two years. "What has been found in virtually every study is that the only way to detect whether someone has worse disease is biopsy, not digital rectal examination or PSA," Dr. Epstein says. "Those measures are not specific enough to identify men who should not be followed on active surveillance."

Dr. Carter says about 1,400 men have been enrolled in the Hopkins active surveillance program at some time since 1995. "Some left the program, others were treated. We know that in the range of 40 percent of individuals who get diagnosed with prostate cancer have favorable disease features. Of those who come to our center who we think qualify for the program about 50 percent enter," Dr. Carter says. Over the past 20 years, he adds, the proportion of men over age 65 who met the criteria for the program who underwent surgery is very small. "We have been very selective about who gets operated and who enters this program," says Dr. Carter.

Asked why they have been more successful than some other urologists at getting men into active surveillance, Dr. Carter says, "It is hard to get into the mind of other people." However, he did suggest that, in part, "There have been particular physicians' concerns about losing an opportunity for cure. And obviously patients' concerns as well. And that affects how physicians communicate the risks of both monitoring and treatment and the balance between the two." Aside from stringent criteria for entry and monitoring, Hopkins has three full-time people who help run the program—a program administrator, a biostatistician, and a biorepository administrator, who manages blood, urine, and tissue.

What are the risks of radical prostatectomy? "Most people who do it all the time would probably conclude that 95 percent of individuals will recover urinary control completely," Dr. Carter says. "Some may claim higher, but I think that's a reasonable estimate." Recovery of erectile function varies. "Under ideal circumstances, which means the patient has no preexisting problem with erectile function, is relatively young, doesn't have extensive disease, and is operated on by someone experienced, I would estimate the chance of getting back to baseline function in the range of 70 percent to 80 percent." Dr. Carter emphasizes the term *baseline function*. "To talk about the return of an erection strong enough for intercourse tells you nothing," he says. That raises questions: Has it happened once? All the time? Are the patient and his partner satisfied with the quality of intercourse?

While the focus has been on urinary incontinence and loss of erectile function, the latter are not the only treatment-related complications, Dr. Carter points out. In a study of the men who underwent surgery or radiotherapy alone for prostate cancer between 2002 and 2009 in Ontario, Canada, almost one in five men were

found to have been readmitted to the hospital with problems related to the surgery or radiation therapy (Nam RK, et al. *Lancet Oncol.* 2014;15:223–231). “Not all the surgeons in the survey met the ‘experienced’ criterion,” Dr. Carter explains. “In the real world most people don’t have access to a surgeon who has done thousands of these operations.”

In the Yale active surveillance program, Dr. Humphrey says, they are not enrolling patients with more than a (3+3) Gleason score. One change at the Yale program is that patients who are being considered for active surveillance undergo a new type of imaging called multiparametric MRI with fusion of ultrasound images. “We perform targeted biopsy of areas that this modality identifies as high-grade cancer,” Dr. Humphrey explains. “Often patients being seen here will already have had a systematic 12-core biopsy. To be sure they are candidates for active surveillance, with low tumor volume and low-grade disease, this multiparametric MRI imaging is done.”

Dr. True

Dr. Humphrey doesn’t have data on how often patients are reclassified at his center on the basis of the new technique, but he refers to published data on this question. At the National Cancer Institute, 1,003 men underwent concurrent MR/ultrasound fusion-guided biopsy as well as standard ultrasound-guided biopsy. “The new method detected 30 percent more high-risk cancers and about 20 percent fewer low-risk cancers, which is exactly what you want,” Dr. Humphrey says (Siddiqui MM, et al. *JAMA.* 2015;313:390–397). “It is not perfect,” he adds, but it could increase accuracy in selecting men for active surveillance programs.

In the University of Washington program, Dr. True says, the criteria for active surveillance are a tumor with no higher Gleason score than (3+4) (more than 95 percent of those in the UW program have Gleason score six cancer) and cancer present in no more than two or three cores of a routine 12-core biopsy. As for how much cancer is present, Dr. True says: “For well over 10 years we have been assessing the amount of cancer by measuring the total amount of parenchyma in which there is cancer with or without intervening tissue. So if there is a focus of cancer at each end of a core, we would say the whole core is positive for cancer.” However, he says, “Gleason score and the number of cores involved are the most important criteria for entry to active surveillance.”

Dr. True says all of his urologic colleagues discuss the active surveillance option with patients and enter patients in the program. “Nonetheless, I know some patients seen here with a diagnosis of prostate cancer, even though they have a minimal-volume tumor and as low grade as it can be, they or their family members are concerned about not treating the cancer and they are reluctant to enter into an active surveillance trial.” There may be uncertainty about how predictive the criteria for entering patients into active surveillance are, he speculates, particularly in the community.

The consensus document cites a half-dozen trials supporting the value of active surveillance. Dr. True points to a multidisciplinary trial headed by urologist Daniel Lin, MD, of the University of Washington, with more than 1,000 patients and follow-up approaching five years that asks an important question: How many patients have a tumor that progresses to a cancer that is found clinically? “I’m not aware of any patient in whom that occurred,” Dr. True says.

“In our active surveillance group, we do have patients who have had prostatectomy and in some of them there are histological features that it is of higher grade or higher stage,” Dr. True says. “But I am not aware of any of those patients having metastases.”

Dr. True has talked with colleagues who themselves have been diagnosed with minimal-risk prostate cancer. “We

talked about the fact that you can't be 100 percent sure the tumor won't progress," he says. "On the other hand, there are side effects, and some are severe enough that the patient should be aware of them. It is a tough decision. Among the colleagues he has talked to, he says, "Some decide to have intent-to-cure therapy; others decide to be followed on active surveillance." It's likely there will always be those who demand action. Even so, the current level of participation in active surveillance can be increased.

"We all recognize we need better tools to distinguish cancers that will not progress if not treated from those that will progress if not treated," Dr. True says.
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Molecular markers to lessen the uncertainty

Dr. Lawrence True, a professor of pathology at the University of Washington and a member of the consensus panel's subgroup on biomarkers, says he is "enthusiastic" about biomarker potential. However, he notes, "We don't have outcomes data to know whether differential expression of markers is associated with different behavior [of prostate cancer] or response to therapy.

Dr. Crawford

"One big advance last year—outside the context of active surveillance—is the discovery of variants of the androgen receptor gene that allow activation of androgen pathways independent of ligand binding to the receptor," Dr. True says. About 10 percent of patients with primary prostate cancer express one of those variants, though at very low levels. Perhaps metastases with those variants will be less responsive to androgen deprivation therapy.

The University of Washington is one of nine centers in a consortium that is looking for biomarkers that correlate with aggressive prostate cancers. Samples taken at radical prostatectomy are examined by tissue microarrays for numerous possible signals. "Two potential markers that have come out so far are loss of PTEN and a high frequency of Ki-67 tumor cells," Dr. True says.

Dr. E. David Crawford, professor of surgery/urology/radiation oncology and head of urologic oncology at the University of Colorado School of Medicine, calls "extremely valuable" a number of prostate cancer markers that have come out in the last few years. He has been using one commercial panel, ConfirmMDx, in the context of patients with a negative biopsy. There are 1.2 to 1.4 million prostate biopsies each year in the U.S. but only about 250,000 cases of prostate cancer.
"Concern about prostate cancer doesn't go away with a negative biopsy," Dr. Crawford says. "If you are biopsied once, you have a 50 percent probability of being biopsied again. And often the second biopsy is negative as well. We want a test that, if it is negative, the patient has a very low probability of having prostate cancer."

Two studies have showed that the ConfirmMDx screen, which measures methylation of three molecules, has a 90 percent negative predictive value. That is, 90 percent of the samples that were negative on this test did not have cancer on subsequent surgery. Both studies were retrospective reviews. Of the 10 percent of patients who were falsely negative, Dr. Crawford says, "Most were Gleason score six."

Dr. Jonathan Epstein, professor of pathology, urology, and oncology at Johns Hopkins, was a co-investigator on one of the studies. He and colleagues recently began to use ConfirmMDx in men with a negative biopsy or high-grade prostatic intraepithelial neoplasia.

“Clinicians are trying to decide whether to leave the patient alone because they have a low risk of cancer or do repeat biopsy,” he says. —*William Check, PhD*

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