Is Repeat Biopsy for Isolated High-Grade Prostatic Intraepithelial Neoplasia Necessary?

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Numerous studies have cited the positive predictive value of isolated high-grade prostatic intraepithelial neoplasia (HGPIN) to the detection of cancer. Epidemiological, morphological, and molecular data support the potential for malignant transformation of HGPIN, yet no current method can discriminate which lesions will progress to clinically significant prostate cancer versus more latent lesions. Recent analyses of multiple retrospective studies have found similar rates of cancer detection following either diagnosis of isolated HGPIN or an initial negative biopsy. This may reflect increased use of extended biopsy techniques involving 10 or more cores rather than the true ability of HGPIN to undergo malignant transformation. This article discusses controversies surrounding management of an isolated diagnosis of HGPIN and whether repeat biopsy of HGPIN should be mandatory or selective in the context of other predictive values such as rising prostate-specific antigen or lesion on digital rectal examination.
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Prostate cancer remains the most common cancer among men in the United States at an estimated incidence of almost 220,000 in 2007.[1] The advent of screening with prostate-specific antigen (PSA) levels and resulting systematic transrectal biopsies has led to an increased detection as well as a downward stage migration.[2] In addition to smaller volume cancers, isolated atypical lesions of the prostate, including prostatic intraepithelial neoplasia (PIN), are commonly detected.

High-grade prostatic intraepithelial neoplasia (HGPIN), historically defined as PIN grades 2 and 3, is characterized by malignant cytologic features of epithelial cells lining benign prostatic acini and ducts.[3,4] HGPIN is described as 4 distinct patterns of tufting, micropapillary, cribriform, and flat, and compelling evidence suggests that it may be a precursor to prostate adenocarcinoma.[5] Abnormal features in HGPIN cells exhibit cytologic and genetic alterations similar to those found in cells from prostatic adenocarcinomas. HGPIN frequently co-localizes with prostate cancer, with associations as high as 85% in peripheral zones.[6,7] Furthermore, PIN precedes development of adenocarcinomas in mouse models of prostate cancer including transgenic adenocarcinomas of the mouse prostate (TRAMP) mice and mice deficient in the tumor suppressor gene phosphatase and tensin homolog deleted on chromosome 10 (PTEN). These correlations between HGPIN and prostate adenocarcinomas have been discussed fully.[6,8]

The number of prostate needle biopsy procedures has risen to approximately 1,300,000 per year.[8] With an incidence of isolated HGPIN on biopsies ranging from 0.6% to 24.6% with a mean of 7.7%, management of HGPIN has widespread implications.[9] Numerous studies have cited the positive predictive value of isolated HGPIN to the subsequent detection of cancer, with rebiopsy schemes ranging from 3 to 12 months following initial diagnosis.[9,10] However, no consensus regarding the frequency and number of repeat biopsies, or whether repeat biopsies are indeed necessary, has been reached. Does the diagnosis of isolated HGPIN warrant the potential rebiopsy of approximately 100,000 men per year in the United States alone, or should more traditional factors such as close monitoring with serum PSA and PSA velocity or change in physical examination justify the need for rebiopsy? This article discusses the controversies surrounding management of an isolated diagnosis of HGPIN and whether repeat biopsy of HGPIN should be selective or mandatory.

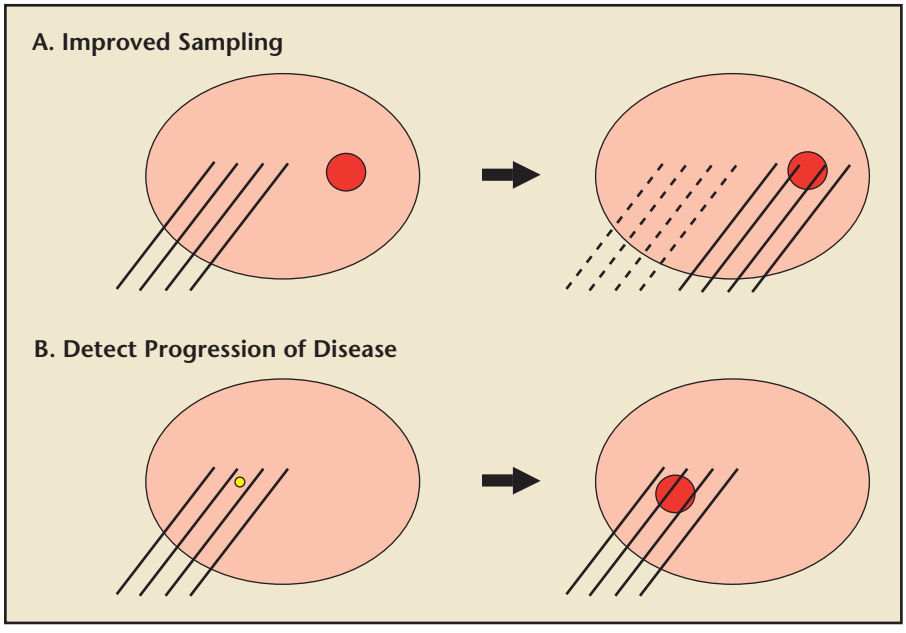
Mandatory Repeat Biopsy of Isolated HGPIN is Unnecessary

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Controversy exists regarding the positive predictive value of HGPIN and utility of repeat biopsy for isolated HGPIN. The rationale for rebiopsy of the prostate is to diagnose missed lesions by improved sampling or to detect progression of disease (Figure 1). Historically, the premalignant potential of HGPIN has prompted urologists to repeat the biopsy, but the evidence to support this recommendation is not so clear. Does repeat biopsy increase the detection of adenocarcinomas in the context of known isolated HGPIN over a benign initial diagnosis? Furthermore, with the unknown natural history and rate of progression of HGPIN, what factors determine the timing of interval rebiopsy in the absence of changes in PSA or digital rectal examination (DRE)? Certain data suggest that mandatory rebiopsy for HGPIN may not be necessary.

To date, localization of prostate cancer by transrectal MRI and MR spectroscopy is in its infancy, and no imaging technique can detect HGPIN. In the absence of a suspicious nodule, systematic transrectal ultrasound (TRUS)-guided biopsy is the gold standard to sample the prostate for a cancer diagnosis. Traditional sextant biopsy strategies have been criticized for high false negative rates by not sampling lateral and transitional zones of the prostate.[11] For this reason, repeat biopsy was frequently performed to detect co-existing prostate cancer following isolated HGPIN on initial sextant biopsy. However, increased sampling improves the detection rate of prostate cancer, with extended biopsies involving 10 or

Figure 1. *Purpose of repeat biopsy is* **(A)** *to improve sampling and detect concurrent cancer, denoted as a red circle, or* **(B)** *to detect progression of disease, from premalignant lesion, denoted as a small yellow circle, to prostate cancer, denoted as a red circle.*



more cores shown to increase detection rates by 15%-30%.[12] There may be a limit to the number of cores needed to decrease sampling error, as saturation biopsy techniques obtaining 14 to as many as 45 cores have not been shown to improve cancer detection compared to 10 cores.[13,14]

As a result, extended biopsy appears to afford reasonable false negative rates that may obviate the need for rebiopsy to detect concurrent cancer despite the predictive association of HGPIN. Multiple studies have produced a broad range of results on detection of cancer by repeat biopsy. In a recent review, the incidence of prostate cancer on rebiopsy following initial diagnosis of isolated HGPIN, performed typically within 1 year, ranged from 2.3% to 100% with a median risk of 24.1%. In comparison, the incidence of cancer detection rates for a repeat biopsy following an initial benign diagnosis ranged from 2.3% to 32.1% with a median of 19%. However, citing studies published in 2000 or later when most studies used extended biopsy sampling, the mean risk of cancer following repeat biopsy is comparable at 18.1% for HGPIN and 23% for benign disease.[9] Thus, in the absence of other predictive values such as rising PSA or lesion on DRE, the finding of HGPIN alone may not justify rebiopsy.

Extended biopsy appears to afford reasonable false negative rates that may obviate the need for rebiopsy to detect concurrent cancer despite the predictive association of HGPIN.

Despite these data, the premalignant nature of HGPIN draws concern and places patients at uncertain risk, although the natural history of HGPIN is unknown. By histology, no current method can discriminate which lesions will progress to clinically significant prostate cancer versus more latent lesions. Few studies have investigated the progression of HGPIN to adenocarcinomas. One such study in a series of 31 patients examined the incidence of prostate cancer on empirical rebiopsy 3 years after an initial diagnosis of isolated HGPIN.[15] These men underwent immediate rebiopsy at the time of diagnosis to minimize the incidence of concurrent cancer. Eight of the men (25%) had prostate cancer with no significant difference in PSA levels. Although the authors concluded that rebiopsy for HGPIN should be performed, it is unclear whether unsampled cancers grew to detectable size on repeat biopsy or there was actual progression of cancer during the 3-year interval.

To date, no randomized trials investigating mandatory repeat biopsy following initial diagnosis of isolated HGPIN versus repeat biopsy for changes in DRE or rising PSA have been performed. Such trials would be prohibitively long to complete. Current evidence does not support mandatory rebiopsy with isolated HGPIN, beyond all patients who have undergone prostate biopsy. Despite extended core biopsies, there will always be a certain number of patients with or without HGPIN who will have cancers missed on initial biopsy due to limitations in sampling and lack of other techniques.

Unfortunately, there is no clear clinical parameter to identify the patient with HGPIN who is more likely to have cancer on repeat biopsy. Evidence to correlate number of cores with HGPIN to risk of cancer is conflicting.[16] With the unknown natural history of HGPIN and the apparent heterogeneity of prostate cancer, clinicians must rely on other traditional approaches of DRE and frequent serum PSA measurements to detect prostate cancer, and even this may not be sufficient. Several studies show that serum PSA levels are not predictive of cancer on repeat biopsy, possibly confounded by missed concurrent cancers versus the *de novo* development. Further studies are needed to determine whether repeat biopsy performed several years following initial diagnosis of HGPIN is necessary in the absence of other indicators. At this point, urologists must consider the informed patient's preferences to dictate an optimal course on an individual basis.

By histology, no current method can discriminate which HGPIN lesions will progress to clinically significant prostate cancer versus more latent lesions.

Isolated HGPIN Requires Mandatory Repeat Biopsy

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HGPIN and, to a lesser extent, atypical small acinar proliferation of the prostate have long been felt to be precursor lesions for prostate cancer. This has been supported by morphological, molecular, and clinical data. For this reason, the current general recommendation is to rebiopsy patients found to have isolated HGPIN on prostate biopsy. Whereas earlier clinical data showed a considerably elevated risk of finding cancer on repeat biopsy in patients with isolated HGPIN, more recent data seem to show a much lower rate of detection. In fact, the rate quoted in recent studies is almost equivalent to the expected incidence of cancer after initial negative biopsy. This would imply

that the progression rate of HGPIN to cancer is no different from the rate of spontaneous *de novo* formation of cancer, thereby bringing into question the need for mandatory repeat biopsy.

Epidemiological evidence shows that HGPIN begins in the third and fourth decades of life and increases with age.[17-19] The prevalence of HGPIN in the general population parallels that of prostate cancer and lags by approximately 5 years, a trend that is expected for a true precursor lesion.[17-19] In addition, multiple autopsy series show a significantly higher prevalence of HGPIN in association with cancer compared with benign glands. An autopsy series of 436 step-sectioned prostates demonstrated an 82% prevalence of HGPIN in association with adenocarcinoma compared with a 43% prevalence in benign prostates.[3] A large autopsy series from Wayne State University, Detroit, MI, looking at men 20 years of age or older who died of trauma showed a significantly higher prevalence of HGPIN in African-American men across all age groups compared with white men, paralleling epidemiological trends identified in prostate cancer patients.[20] In addition, HGPIN lesions were more extensive at younger ages in African-American men.

Morphological and histological data also support the concept of HGPIN as a premalignant lesion. HGPIN glands demonstrate marked cytologic atypia, uniform nuclear enlargement, and prominent nucleoli, similar to invasive prostate cancer.[3,4] HGPIN is also commonly multifocal, occurring predominantly within the peripheral zone and often in close proximity to prostate cancer.[6,7]

HGPIN and cancer exhibit numerous similar changes at the molecular level. Notably, gain of chromosomes 7q31 and 8q and multiple copies of the c-myc genes, as well as loss of chromosomes 10q, 16q, and 18q are all common to both.[21-23] Telomerase is required for persistent proliferation of cells. Normal healthy prostate glands show a lack of telomerase, consistent with a differentiated, non-proliferative state, whereas HGPIN and cancer both show higher levels of telomerase.[24,25] Additional indices of proliferation and apoptosis as well as assessments of cell cycling abnormalities further confirm the link between HGPIN and prostate cancer.[26-30]

Whereas earlier studies quoted the risk of detecting cancer on repeat biopsy for HGPIN to be in the range of 27% to 79%,[10,31-35] larger and more recent studies quote a risk of 23% to 32.2%.[36-39] In those with 50 or more patients, the median risk approaches 25%. This must be compared with the risk of detecting cancer on repeat biopsy after an initially negative biopsy. In 1 series of patients with a persistently elevated PSA and either an abnormal DRE or TRUS with an initial benign biopsy, the risk of cancer on repeat biopsy was 19%, rising to 24% on repeat biopsies.[40] This is similar to other studies, which have quoted approximately 20% risk of subsequent cancer detection after an initial benign biopsy. Of 22 publications since the year 2000 looking at the rate of cancer detection following the finding of isolated HGPIN, 16 (73%) report a risk of 24% or less.[9] Seven out of 9 papers that compared risk of cancer on rebiopsy for isolated HGPIN versus initial benign biopsy found no statistically significant difference.[9] By this argument, if we rebiopsy patients with isolated HGPIN, we may as well rebiopsy all patients with initial negative biopsy in the setting of abnormal DRE or elevated PSA. The flaw in this logic, however, can be understood if we examine the likely cause of the decreased rates of cancer detection on rebiopsy for HGPIN seen in later studies.

In the PSA era there has been a notable stage migration to smaller, lower-grade, more likely organ-confined disease. Partly due to a heightened awareness of prostate cancer and partly due to improved biopsy techniques, we are missing fewer and fewer cancers, including those associated with HGPIN. Whereas we were missing more concurrent cancers with older sextant biopsy techniques, we are now detecting these cancers with the more frequent use of extended biopsy techniques. Consequently, the detection rate of cancer on repeat biopsies has gone down.

This point was reiterated in a study that Herawi and colleagues conducted on a large group of men who underwent rebiopsy following diagnosis of isolated HGPIN.[41] They closely examined the relationship between cancer detection on repeat biopsy and the number of cores sampled. For patients undergoing sextant biopsy on initial and repeat biopsy, the risk of cancer on rebiopsy was 14.1%. When initial sextant biopsy was followed by $>$ 8 cores on repeat biopsy, the detection rate went up to 31.9%. With $>$ 8 cores for both initial and repeat biopsy, the detection rate was again 14.6%. This suggests that poor sampling at initial and repeat biopsy misses potential concurrent cancers. With poor sampling on

Multiple autopsy series show a significantly higher prevalence of HGPIN in association with cancer compared with benign glands. . . . Morphological and histological data also support the concept of HGPIN as a premalignant lesion.

initial biopsy followed by better sampling, more of the concurrent cancers are detected. When extensive sampling is performed initially, a greater number of the concurrent cancers are detected, such that when isolated HGPIN is diagnosed, it is more likely to truly represent isolated HGPIN.

Decreased rates of cancer detection on rebiopsy for isolated HGPIN, therefore, likely represent a sampling artifact with increased detection of concurrent cancers by extended biopsy techniques. This phenomenon, however, does not take into consideration the possibility of malignant transformation of HGPIN over time. Similarly, it is difficult to distinguish whether cancer detection rates following initial negative biopsy reflect a sampling artifact or true *de novo* formation of cancer. In fact, the likelihood of missed cancer at initial biopsy in this group may not be insignificant considering the higher baseline risk of cancer in this population with elevated PSA or abnormal DRE compared with the general population. Therefore, a comparison in cancer detection rates on rebiopsy for patients with isolated HGPIN versus those with initial negative biopsy may not adequately address the question of whether rebiopsy should be performed for isolated HGPIN. The true question should be: "Does isolated HGPIN progress to prostate cancer with a frequency higher than the rate of true de novo formation of cancer in the absence of sampling artifact and missed concurrent cancer?" If the answer is yes, then repeat biopsy is warranted in the setting of isolated HGPIN.

The answer to this question requires further studies and investigation, but analysis of the data on timing of repeat biopsy following a diagnosis of isolated HGPIN provides some useful information. Although there is debate as to the timing of repeat biopsy, the ideal time would allow for the natural progression of HGPIN to prostate cancer. Lefkowitz and associates reported that repeat biopsy in patients with HGPIN resulted in a 2.3% cancer detection rate if performed within 1 year of initial biopsy,[42] but repeat biopsy of the same patient population 3 years after initial biopsy demonstrated a significantly increased detection rate of 25.8%.[15] Roscigno and colleagues reported a similar trend but overall higher detection rates on repeat biopsy with a 25% rate if rebiopsy was within 6 months and 44.6% if rebiopsy was within 11.4 months of initial biopsy.[43] These studies support the concept that HGPIN is a precursor lesion that can progress to prostate cancer. Similar studies involving early and delayed rebiopsy following an initial negative biopsy utilizing extended biopsy techniques would further elucidate whether rebiopsy for isolated HGPIN is truly warranted. However, the data presented here combined with epidemiological, histological, and molecular data provide strong evidence for the potential for malignant transformation of HGPIN. Consequently, if the ultimate goal is to maximize cancer detection, the finding of isolated HGPIN should prompt rebiopsy regardless of PSA.

When extensive sampling is performed initially, a greater number of the concurrent cancers are detected, such that when isolated HGPIN is diagnosed, it is more likely to truly represent isolated HGPIN.

The timing of rebiopsy, however, remains controversial and should be considered within the overall clinical context, keeping in mind that the ultimate goal is to efficiently detect progression of HGPIN to cancer without sacrificing cancer-specific mortality from potentially missed high-risk disease. Isolated HGPIN on an initial extended biopsy likely represents true isolated HGPIN with a small chance of having a concomitantly missed tumor. These potentially missed tumors, however, are much more likely to be small, lower-grade, and organ-confined rather than locally advanced or high-grade. If rebiopsy is performed early, detection of these potentially missed small tumors would likely increase, but the malignant transformation of HGPIN may not be detected. In contrast, if rebiopsy is delayed, detection of the malignant transformation of HGPIN would be increased significantly while possibly allowing for the progression of potentially missed tumors. It could be argued, however, that these missed tumors would be unlikely to be locally advanced even at the time of delayed rebiopsy. This reasoning favors delayed rebiopsy and is supported by the Lefkowitz group's research, which showed that all patients found to have prostate cancer on delayed rebiopsy 3 years following a diagnosis of isolated HGPIN who subsequently underwent radical prostatectomy had organ-confined disease.[15]

Decreased rates of cancer detection on rebiopsy for isolated HGPIN, therefore, likely represent a sampling artifact with increased detection of concurrent cancers by extended biopsy techniques.

Opponents of mandatory repeat biopsy argue that the decision to rebiopsy patients should be made purely based on changes in PSA or DRE, irrespective of the presence of HGPIN. This approach seems to refute the thinking that HGPIN is a premalignant lesion known to progress to prostate cancer. In fact, looking at patients who underwent delayed rebiopsy for HGPIN, there was no association on univariate regression analysis between change in PSA and detection of prostate cancer, suggesting that patients who had progression of HGPIN to prostate cancer had a similar change in PSA of an average of 1 unit compared with those who had negative rebiopsies after 3 years.[15] As such, the use of PSA and/or DRE alone may not take into consideration the subset of patients who may have progression from HGPIN to cancer in the absence of PSA elevation or change in clinical examination. This is particularly relevant, considering the fact that a significant number of cancers are detected in patients with PSA values less than 4.[44] Additionally, DRE is known to have both a limited sensitivity and limited positive predictive value for detection of cancer.[45] If the ultimate goal is maximizing cancer detection, then identification of isolated HGPIN should be indication enough for repeat biopsy in addition to changes in PSA or DRE.

Although controversy exists as to whether repeat biopsy should be mandatory for isolated HGPIN, it is clear that there are certain subsets of patients who would have improved cancer detection by undergoing rebiopsy. Persistent presence of HGPIN on first rebiopsy has been shown to correlate with increase in cancer detection rates. Gokden and colleagues found that PSA and age were independent risk factors for subsequent diagnosis of prostate cancer, but the presence of HGPIN and the number of cores affected by HGPIN were not.[37] If, however, HGPIN was detected on the first repeat biopsy, the subsequent cancer detection rate was 41% compared with 18% if the first rebiopsy was benign.[37]

In contrast to that study, several others have shown a significant correlation between the number of cores with HGPIN and subsequent cancer detection. A recent study by Netto and Epstein looked at widespread HGPIN, defined as 4 or more positive cores, in 41 patients and found a subsequent cancer detection rate of 39%.[16] When further stratified by age, those patients with widespread HGPIN over the age of 70 had a 55% rate of cancer detection on subsequent biopsies. A study by Kronz and colleagues showed significant correlation between number of cores affected by HGPIN and subsequent cancer detection on repeat biopsy.[38] Patients with 1-2 cores, 3 cores, or $>$ 3 cores with HGPIN had subsequent cancer detection rates of 30.2%, 40%, or 75% respectively. Additionally, among 81 patients who underwent multiple repeat biopsies, risk of subsequent cancer detection was 10% if the first repeat biopsy was benign and 25.9% if HGPIN was diagnosed. This study and others have also shown that if more than 2 repeat biopsies are performed, the risk of subsequent cancer detection is relatively insignificant.

Epidemiological, morphological, and molecular data clearly indicate an important correlation between HGPIN and prostate cancer, with strong evidence supporting the potential for its malignant transformation over time. There is additional clinical and autopsy data supporting the clear association between HGPIN and prostate cancer. The current controversy regarding the need for mandatory repeat biopsy for HGPIN stems from recent analyses of multiple retrospective studies showing similar rates of cancer detection following diagnosis of isolated HGPIN and following an initial negative biopsy. These studies, however, are not prospective and not standardized in terms of the method of biopsy and the timing of repeat biopsy, thereby making it impossible to draw any conclusions regarding the need for repeat biopsy for HGPIN. These data may be obscured by the possibility of sampling artifacts and inconsistencies of biopsy method and timing between studies. Clinical studies better designed to answer the question of whether HGPIN progresses to prostate cancer have examined the rates of cancer detection on early and delayed repeat biopsy for HGPIN following initial extensive sampling, with results consistently confirming the likely ability of HGPIN to progress to cancer irrespective of changes in PSA. Similarly designed prospective studies comparing rates of progression of HGPIN to cancer to rates of *de novo* cancer formation following an initial negative biopsy may provide further information regarding the need for repeat biopsy following a diagnosis of isolated HGPIN.

In conclusion, current trends in decreased cancer detection rates on repeat biopsy following diagnosis of isolated HGPIN may reflect changing biopsy practices toward the use of extended biopsy techniques rather than the true ability of HGPIN to undergo malignant transformation. There is a clear association between HGPIN and prostate cancer with several clinical studies demonstrating the potential for malignant transformation over time in the absence of significant changes in PSA. This is reason enough to perform repeat biopsy after a finding of isolated HGPIN. Although timing of rebiopsy remains controversial, it is clear that initial and repeat biopsies should involve an extended

biopsy technique. Rebiopsy within 6-12 months of initial diagnosis may increase detection of missed concurrent cancer in patients with inadequate sampling on initial biopsy, whereas delayed biopsy should detect cancers that develop by malignant transformation of HGPIN. The presence of widespread HGPIN involving multiple cores, especially in the setting of age > 70 or the presence of HGPIN on first repeat biopsy should unequivocally warrant repeat biopsy. ■

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Main Points

- Use of prostate-specific antigen (PSA) has led to earlier detection of prostate cancer and a notable stage migration to smaller, lower-grade, more likely organ-confined disease. Consequently, the detection rate of cancer on repeat biopsies, including those prompted by diagnosis of high-grade prostatic intraepithelial neoplasia (HGPIN), has gone down.
- Traditional sextant biopsy strategies have been criticized for high false negative rates by not sampling lateral and transitional zones of the prostate. Extended biopsies involving 10 or more cores have been shown to increase detection rates by 15%-30%.
- Multiple autopsy series show a significantly higher prevalence of HGPIN in association with cancer compared with benign glands. Morphological and histological data also support the concept of HGPIN as a premalignant lesion.
- No current method can discriminate which HGPIN lesions will progress to clinically significant prostate cancer versus more latent lesions.
- Randomized trials investigating mandatory repeat biopsy following initial diagnosis of isolated HGPIN versus repeat biopsy for changes in digital rectal examination or rising PSA would be prohibitively long to complete.

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