International Society of Urological Pathology Consensus on Cancer Precursor Lesions. Working Group 1

The Prostate

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Abstract: Working Group 1 at ISUP's Cancer Precursors meeting (September 2024) evaluated 5 putative precursors of invasive prostate cancer: high-grade prostatic intraepithelial neoplasia (HGPIN), intraductal carcinoma (IDC), atypical intraductal proliferation (AIP), atypical adenomatous hyperplasia (AAH)/adenosis, and proliferative inflammatory atrophy (PIA). Objectives were to compile recent evidence, interrogate current practices, and vote on recommendations, with 67% approval defined as consensus. Consensus was reached against the reporting of the low-grade form of PIN. HGPIN need not be reported when concomitant cancer or atypical small acinar proliferation suspicious for cancer exists adjacent to it, for biopsy or prostatectomy specimens. Finally, while the clinical significance of unifocal HGPIN in biopsies remains uncertain, there is stronger evidence for multifocal isolated HGPIN as a predictor of subsequent cancer detection. By consensus, multifocal HGPIN should continue being reported. Slight refinement was achieved regarding IDC criteria. The consensus opinion was that a dense cribriform to solid proliferation need not demonstrate marked nuclear atypia/ pleomorphism to qualify as IDC. The inverse scenario of marked atypia without dense cribriform/solid proliferation fell just short (65%) of consensus for IDC. Redesignating cribriform HGPIN as AIP achieved consensus. AIP found alone or with grade group 1 cancer warrants an explanatory comment. However, agreement was not attained to report AIP in the presence of invasive cancer, in either needle biopsy or prostatectomy. Finally, the optional reporting of PIA or AAH/adenosis in biopsies as pertinent negatives both fell short of consensus. This guidance should help pathologists standardize reporting, staying focused on the clinically actionable aspects of these lesions.

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Conflicts of Interest and Source of Funding: N.A.'s institution has received research funding from Arnivas, Astellas, AstraZeneca, Bayer, Bristol Meyers Squibb, CRISPR Therapeutics, Eisai, Eli Lilly, EMD Serono, Exelixis, Genentech, Gilead, Glaxo Smith Kline, Immunomedics, Janssen, Lava, Merck, Neoleukin, Novartis, Oric, Pfizer, Roche, Sanofi, and Seattle Genetics. For the remaining authors none were declared.

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Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.ajsp.com.

DOI: 10.1097/PAS.0000000000002430

Key Words: prostate, precursor lesion, consensus conference, prostatic intraepithelial neoplasia, intraductal carcinoma, atypical intraductal proliferation

(*Am J Surg Pathol* 2025;00:000–000)

Recent research on intraepithelial lesions that at times may be precursors of invasive prostatic adenocarcinoma has advanced at a brisk pace, creating a knowledge deficit among pathologists. Five types of prostatic lesions have some evidence to support a precursor role. The first to be recognized, and the best-characterized regarding etiology and progression, is prostatic intraepithelial neoplasia (PIN), chiefly its high-grade (HG-) form. A second lesion that has gained attention relatively more recently is intraductal carcinoma (IDC), with its marked architectural and cytologic atypia. Third is atypical intraductal proliferation (AIP), a designation reserved for lesions with features intermediate between HGPIN and IDC. Fourth, atypical adenomatous hyperplasia (AAH)/adenosis is a candidate precursor of some low-grade cancers. Finally, proliferative inflammatory atrophy (PIA) is the least well-characterized in terms of being a direct carcinoma precursor. A consensus conference was undertaken to review recent findings and help to clarify the current understanding.

METHODS

In preparation for the ISUP Consensus Conference on Cancer Precursor Lesions, we organized Working Group 1 (prostate), comprising the authors of this paper. All but 3 were pathologists, and the others were a medical oncologist (N.A.), a urologist (G.G.), and a basic scientist (T.R.). A premeeting survey was circulated in summer 2024 to interrogate current practice by the ISUP membership and drew 142 responses (Supplementary File 1, Supplemental Digital Content 1, http://links.lww.com/PAS/C124).

The ISUP Consensus was held in Florence, Italy, on September 12, 2024. The group was tasked with reviewing the survey findings and literature with the following objectives: give presentations on the evidence supporting a precursor role of each lesion, their diagnostic criteria, and their clinicopathologic significance. Working groups were also asked to design questions for electronic voting (using a commercial software package called PollEverywhere) at the meeting to support recommendations for practice and to facilitate discussion by presenters and participants at the meeting. A 67% approval was defined as consensus.

RESULTS

One hundred eleven voting subspecialized urologic pathologists attended the meeting. The average number of respondents to a voting question was 93 (range 89 to 99; Supplementary Data, Supplemental Digital Content 1, http://links.lww.com/PAS/C124). Pathologists were 90% academic-affiliated from North America (44.7%), Europe (44.0%), Asia (4.3%), South/Central America (3.5%), and Australia (3.5%).

HPGIN

Historical Description and Predictive Significance

While intraepithelial lesions resembling PIN were described previously in the literature under various names, McNeal and Bostwick first enumerated specific diagnostic criteria in 1986, referring to the lesion as intraductal dysplasia,[1] which was subsequently termed PIN in 1987.[2] PIN is morphologically defined as the presence of neoplastic appearing cells, characterized as luminal epithelial cells with nuclear and nucleolar enlargement, and occurring withing pre-existing ducts and acini of the prostate. Often, there is attenuation and/or partial loss of a basal cell layer.[3] It bears a strong spatial relationship to invasive cancer: in a digital-based prostatectomy study, 363 HGPIN foci either abutted or came within 2 μm from invasive cancer in 90% of instances.[4] Three grades of PIN were initially described according to degree of atypia, with PIN1 being low-grade and PIN 2 or 3 being high grade[5]; however, low-grade PIN is not currently diagnosed by pathologists in clinical samples due to low interobserver reproducibility and lack of predictive power for a subsequent cancer diagnosis.[6] Four architectural patterns of HGPIN were described in 1993: the most common is tufted, then micropapillary, flat, and cribriform (Figs. 1A–D).[3] These 4 were thought to have the same biologic potential,[7] although recent studies have provided early evidence that micropapillary[8] may have molecular features of a more aggressive form. Also, the World Health Organization endorses that what was formerly called cribriform PIN should now be referred to as AIP,[9] which is clinically more concerning than PIN and is discussed below.

According to autopsy studies, >40% of men in their 40s have some HGPIN.[10] As expected, sets of needle biopsies allow a much lesser extent of sampling, so the incidence of isolated HGPIN (no concomitant cancer detected) on biopsy is much lower, ranging from 1.7% to 16.5%.[11] Historically, the clinically relevant emphasis for isolated HGPIN was that its presence on needle biopsy was associated with an increased risk of finding cancer (clinically significant or not) on repeat biopsy. Subsequently, over time, numerous studies demonstrated that this predictive value has declined from ~45% in the 1990s to ~25% in recent years (Fig. 2).[11–53] By 2005, a meta-analysis disclosed that the mean predictive value had fallen from 36% in studies from before 1995 to 22% after 2000.[25] These numbers approach the 19% to 26% risk[17,53] of finding cancer on repeat biopsy for men with elevated PSA, without high grade PIN, after an initial negative biopsy. Moreover, HGPIN accompanies less-aggressive cancer: In 901 radical prostatectomy tissues, among 589 followed-up patients with intraductal proliferative lesions, HGPIN (by multivariate analysis) independently predicted infrequent biochemical recurrence.[54]

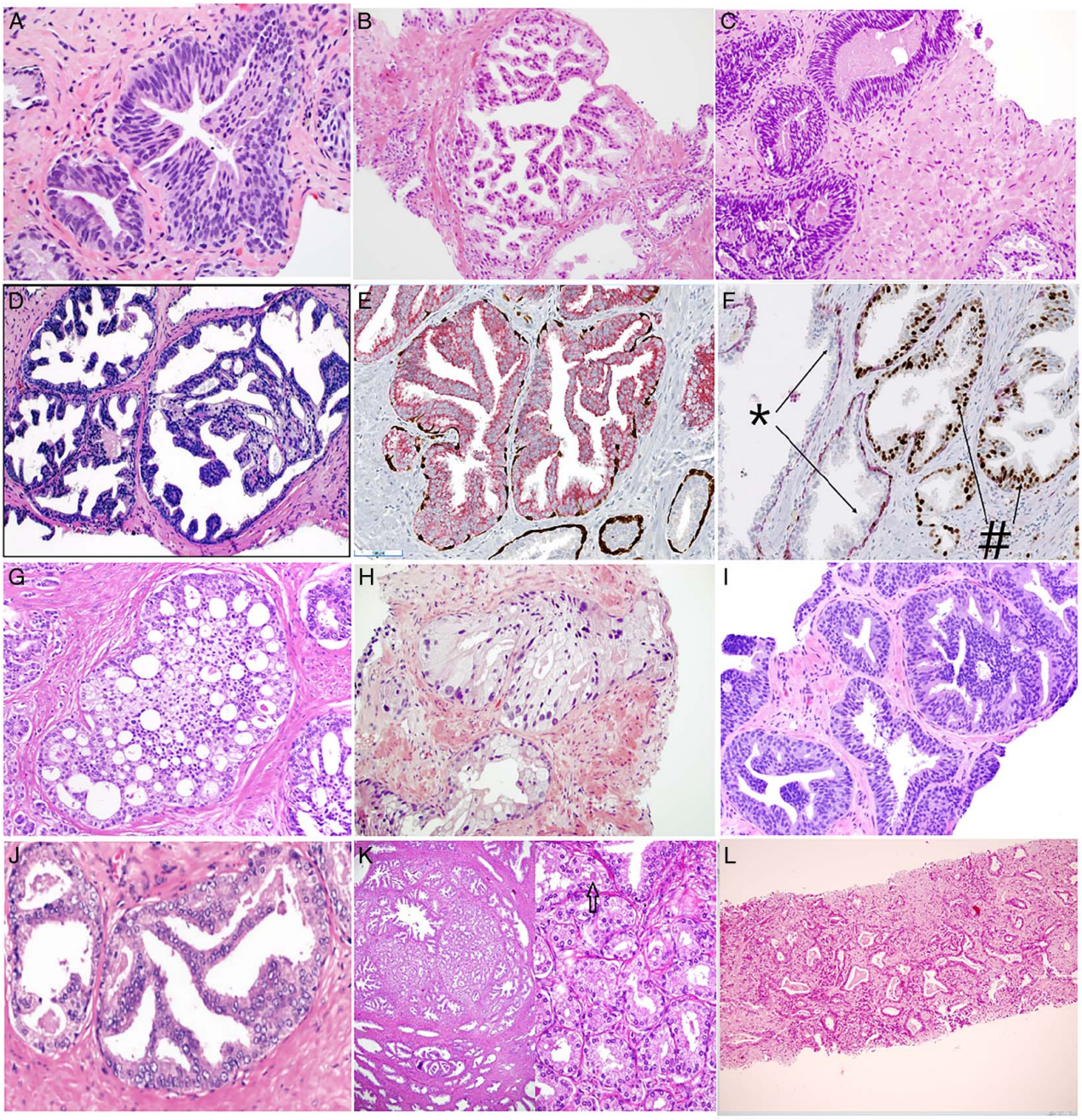

FIGURE 1. A, Tufted pattern of HGPIN is the most common of its 4 patterns. B, Micropapillary pattern of HGPIN features filiform structures lacking a fibrovascular core. C, Flat pattern of HGPIN is seen in acini at the top of the image. D, Cribriform pattern of HGPIN was, by consensus, redesignated as atypical intraductal proliferation (AIP). E, By triple (cocktail) immunostain, HGPIN characteristically retains at least a patchy basal cell layer (brown, high molecular weight cytokeratin and p63) while showing increased AMCR (red, also called P504S), similar to cancer cells. F, Situated adjacent to HGPIN (#, with brown MYC protein overexpression), the normal-appearing acini (*) show partial loss of red Glutathione S-transferase (GSTP1) through promoter hypermethylation. This signals susceptibility to oxidative stress-induced DNA damage, likely an important step in carcinogenesis. G, Intraductal carcinoma (IDC) with usual cribriform pattern. Small, dense basal cells are evident at the periphery. H, Marked nuclear enlargement alone is often found in IDC, but it is not sufficient as a sole criterion for IDC. I, Atypical intraductal proliferation (AIP) demonstrates features intermediate between HGPIN and IDC. This cribriform proliferation shows high cellularity but minimal atypia. J, AIP, showing less cellularity but more nuclear atypia, with nuclear clearing. K, Atypical adenomatous hyperplasia (AAH/adenosis) occurs as part of a BPH nodule (left). It lacks atypia and shows a corpus amylaceum (arrow). L, Proliferative inflammatory atrophy has acini with diminished cytoplasm and reactive features in an inflammatory background.

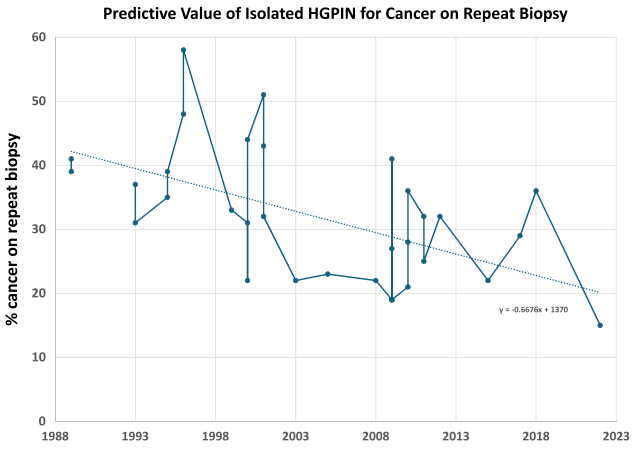

FIGURE 2. Time-wise decline in the predictive value of isolated high-grade PIN (HGPIN) for all cancers on repeat biopsy.

It is likely that the predictive power of HGPIN for subsequent cancer was initially higher because PSA testing was first introduced among a population not previously tested, and thus that population contained many patients who already had cancer. The presence of isolated HGPIN was likely serving as a marker for patients with existing cancer. However, after multiple rounds of screening, many of the men with larger cancers were removed from screening because they were found to have cancer. The remaining men with HGPIN had a lower prevalence of unsampled cancer, which may have resulted in decreased predictive power of HGPIN for subsequent cancer. In addition, changes in practice patterns may also account for this decreased predictive power owing to the increasing use of PSA fractionation and then extended biopsy sampling techniques in the 2000s ($\geq$12 cores or sites). More robust biopsy schemes likely resulted in more accurate initial cancer diagnoses and hence led to lower cancer detection rates following an isolated HGPIN diagnosis. More recently, this decline has been accelerated by wider use of MRI-targeted (fusion) biopsies. These targeted biopsies show greater sensitivity for cancer, particularly clinically significant cancer, resulting in fewer negative biopsy sets. Finally, some of what is now designated AIP or IDC was probably HGPIN in decades past. As a result of these developments, the rate of repeat biopsy for HGPIN by urologists, which was 40% to 71% up until 2015,[32,44–46] has trended down to $\leq$36% in recent studies.[34,42,43] The Early Detection of Prostate Cancer Panel of the American Urological Association/Society for Urologic Oncology (AUA/SUO) in 2023 issued a Moderate Recommendation (Evidence Level: Grade C) saying that immediate repeat biopsy need not be performed for unifocal HGPIN, but routine follow-up is sufficient.[43]

Multifocality of HGPIN has been emphasized as influential by several of these studies. It had been known since 2000 that the location of cancer detected on repeat biopsy was often not the same biopsy site as the HGPIN.[44] Of note, the presence of isolated HGPIN on multiple cores was a stronger and more consistent predictor of cancer than its presence on a single core (Fig. 3).[25,26,28,39,40,47] Thus, HGPIN on multiple cores approaches the 39% to 45% predictive value of atypical small acinar proliferation suspicious for cancer (ASAP).[25] This suggests that a recommendation for a repeat biopsy after multifocal HGPIN is more relevant than after single-core HGPIN. However, it may be argued that >50% of cancer detected after multifocal HGPIN was considered not clinically significant,[47] and in three studies that evaluated the grade of cancer after HGPIN it was grade group 1 (Gleason 3 +3) cancer, in 75%, 64%, and 58% of studied cases.[26,28,40] The position taken by the AUA/SUO is that even multifocal HGPIN alone may not be an indication for repeat biopsy, but that other findings should be considered.[43] Overall, the evidence establishes HGPIN as a candidate precursor to many invasive adenocarcinomas. Yet, given that it is also the likely precursor to many low-grade, possibly clinically insignificant cancers, and that its value as a predictor of clinically significant cancer in subsequent biopsies is very limited,[43,45] it seems unwarranted to give an unequivocal recommendation for repeat biopsy after its diagnosis on needle biopsies.

Molecular Findings

Many of the key molecular alterations known to drive the development of invasive adenocarcinoma are present in at least some HGPIN lesions. However, oncogenic alterations in the genomic structure and gene expression tend to occur in HGPIN at a rate lower than for invasive cancer. Detailed reviews are available[3,55–59]; but Table 1 enumerates a number of pertinent study findings.[60–80] Most relevant for diagnostic pathologists, the commonly used "triple cocktail" usually shows an increase in α-methylacyl coA racemase (AMACR) expression in HGPIN nearly equivalent to that of cancer, although with at least focally retained basal cell marker expression (Fig. 1E). Glutathione S-transferase-π (GSTP1) loss due to promoter hypermethylation is an early step in prostate cancer development in >90% of cases,[77] and Figure 1F shows complete GSTP1 expression loss in HGPIN, with partial loss in adjacent benign PIA acini.

Practical Perspective on HGPIN

Three considerations dampen the present-day importance of reporting isolated HGPIN as a cancer precursor: (1) it is most prevalent in elderly patients, (2) evolution to clinically significant cancer may or may not occur, and (3) such evolution may take many years. Its main utility for clinicians, then, has been as a surrogate marker for missed cancer. However, in the MRI era, some cancers that would have been previously missed with blind biopsy are now often apparent on MRI, and nearly all the above papers reporting a predictive value for HGPIN preceded the era of widespread MRI use. Remarkably, multiparametric (mp)MRI has diminished the importance of biopsy findings in general, and in one study emerged as the only predictor of clinically significant cancer, when compared to lesions such as HGPIN and ASAP, suspicious for cancer.[47] In that controversial study, 56 patients

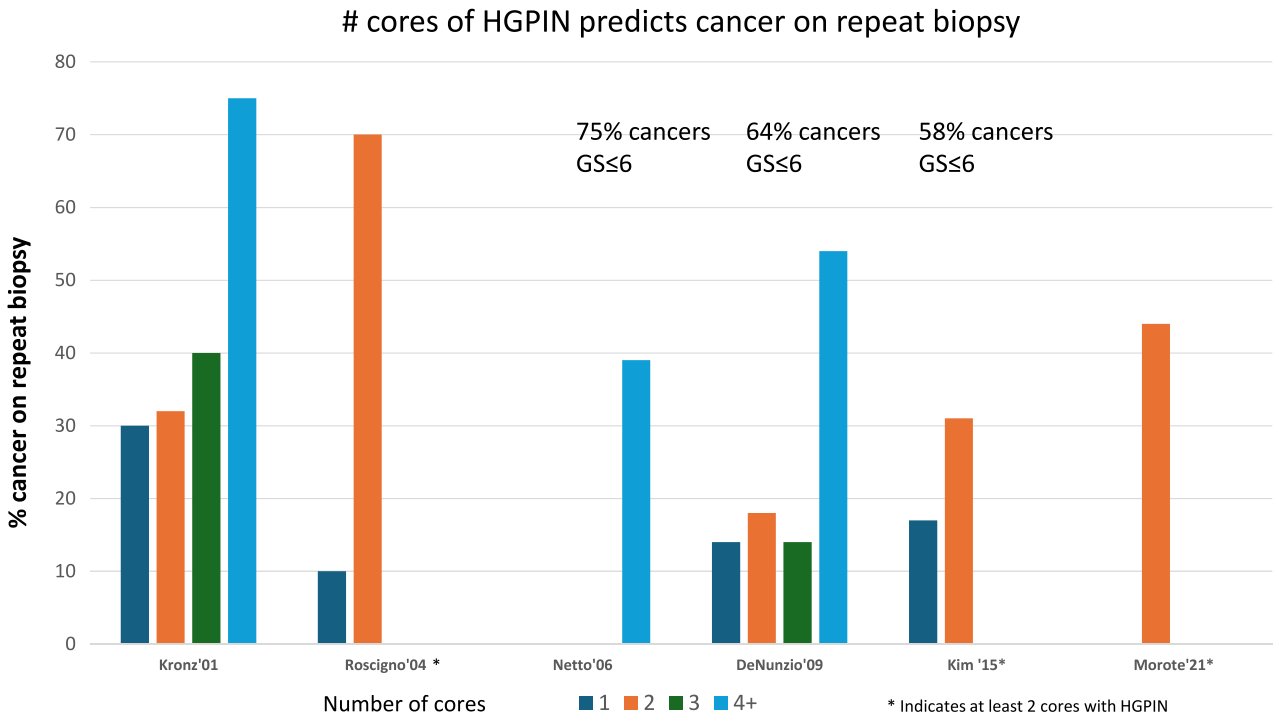

FIGURE 3. Multi-core HGPIN shows a distinctly higher predictive value for cancer on repeat biopsy than single-core HGPIN. GS indicates Gleason score.

underwent radical prostatectomy based solely on PSMA PET/CT and multiparametric (mp)MRI findings, without a preoperative biopsy. One patient (1.8%) had benign disease, while 6 (10.7%) had clinically insignificant cancer of grade group <2.[82] However, radiographic techniques cannot detect and grade cancer sensitively enough to make this standard practice.

Given all these considerations, some consensus conference participants advocated de-emphasizing HGPIN by removing it from the top-line diagnosis and

TABLE 1. Original Studies on Molecular Alterations in HGPIN

Finding	References
Aneuploidy, but not as much as in INV	3,58
8q24 chromosome gain (affecting MYC oncogene) and FOXA1 mutation, same as INV, but fewer total mutations and CNVs by whole-exome sequencing	61
This MYC causes prominent nucleoli, multiple nucleoli, and higher rRNA levels	62
MYC nuclear RNA and protein overexpression in at least 76% up to 95% of lesions	57,63
8p chromosome LOH in 63% of foci vs. 91% for INV; manifest as nuclear NKX.3.1, a tumor suppressor	64
Telomere shortening by FISH in 68%-93% of HGPIN, but almost all INV	65,66
Telomere shortening by FISH in 32%-68% of vs. 83%-85% in INV	67
MYC stimulates hTR in both HGPIN and INV, as confirmed by silencing and overexpressing MYC	68
Increased mitochondrial DNA copy number, but not as much as INV	69
TMPRSS2-ETS family (ERG) fusion in 11%-19%, vs. about half of INV	70,71
The above fusion, when in isolated HGPIN, predicted subsequent INV detection	71
PTEN loss in 8% of cases. However, in cystoprostatectomy, no PTEN loss but ERG fusion in 7% of isolated foci	72,73
5'ETS 45S rRNA signal elevated in HGPIN and INV by in situ hybridization, compared with benign epithelium	74
SPINK1 overexpression in 5%, vs. 11-15% of INV; usually exclusive to ERG rearrangement and exclusive with bialleic PTEN loss	75
Numerous epigenetic changes	76
CpG island methylation of tumor suppressor genes APC, GSTP1, MGMT, and RASSF1A in ~30%, less than the 57%-83% for INV	77
GSTP1 loss by CpG promoter hypermethylation in 69% vs. 91% for INV	78
GSTP1 promoter methylation using bisulfite sequencing showed high prevalence in HGPIN and INV with evidence of partial methylation and progressive spreading on individual alleles from HGPIN to INV. No methylation in normal and less dense CpG methylation present in some PIA, especially those near INV.	79
RAR β2 hypermethylation in 95% of HGPIN and 98% of INV	80

CNV indicates copy number variation; ERG, ETS-related gene; GSTP1, glutathione S-transferase-π; hTR, human telomerase RNA; INV, invasive carcinoma; LOH, loss of heterozygosity; PIA, proliferative inflammatory atrophy; PTEN, phosphatase and tensin homolog; RAR β2, retinoic acid receptor beta2; SPINK1, serine protease inhibitor Kazal type I.

reporting it in a microscopic description or comment. The current recommendation, therefore, is that the choice to continue reporting it as a top-line diagnosis should rest with the individual pathologist. In settings in which there is frequent communication with clinicians, this decision may be most appropriately made after discussion with the urologists and/or radiation oncologists at one's institution.

Histologically, the differential diagnosis includes basal cell hyperplasia with prominent nucleoli (the most common mimic), PIN-like adenocarcinoma, and AIP (see below). A newly described mimic is circumferential perineural invasion. This can distort invasive cancer acini such that they mimic HGPIN (Fig. 4), which may require immunostains to sort out.

Consensus Voting

In the premeeting survey, we asked about the preferred term for reporting HGPIN. Some pathologists have suggested dropping "high-grade" since this name sounds worrisome to patients. However, most respondents (89%) favored no change, with only 11% favoring just "prostatic intraepithelial neoplasia." In the premeeting survey, 88% would report unifocal or multifocal HGPIN. Also, 89% did not include a comment recommending repeat biopsy for isolated HGPIN.

At the meeting (Table 2), for both biopsy and prostatectomy specimens, strong support emerged that reporting of HGPIN is not mandatory when concomitant cancer or ASAP suspicious for cancer was present. Regarding unifocal HGPIN, its clinical significance is unclear, and the working group members could not agree on a recommendation. Thus, at the meeting, we chose not to have a voting question on the reporting of unifocal HGPIN. Question 5 asked only about the reporting of multifocal isolated HGPIN in biopsies, and respondents strongly endorsed it. Finally, consistent with WHO recommendations,[55] the former cribriform pattern of HGPIN should be redesignated AIP.

Intraductal Carcinoma (IDC)

The term IDC was first used in 1985, as "spread of carcinoma by way of the ducts,"[83] predating the wide recognition of PIN. HGPIN grade 3 was initially equated to carcinoma in situ,[2] although the concept of IDC was not publicized, largely keeping IDC under the HGPIN rubric. In 1996, IDC was noted in 51 radical prostatectomy cases[84] as a lesion separate from (but often mingled with) dysplasia, the authors' term for HGPIN. Despite these early descriptions, IDC was not recognized by the World Health Organization[9] until 2016. This followed a torrent of studies that recognized the association of IDC with adverse pathology and clinical outcomes.

The definition of IDC has been somewhat controversial. However, most studies agree that IDC is a lesion that distends a duct space (ie, is bounded by basal cells) and has a proliferation of moderately to very atypical cells, which may be punctuated by cribriform spaces (Fig. 1G), verging on a solid pattern. In the absence of solid or dense cribriform architecture, it has also been proposed that lesions with loose cribriform or micro-

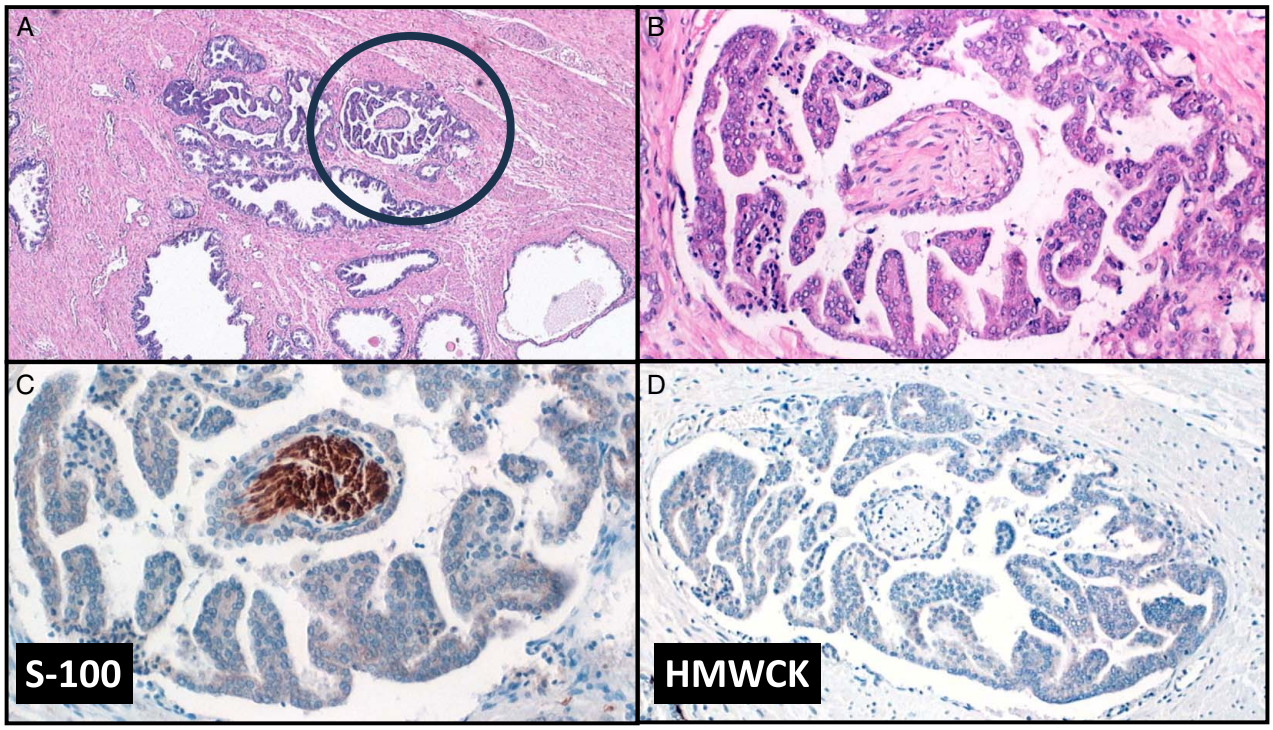

FIGURE 4. Perineural invasion by cancer may sometimes mimic HGPIN (A, B), but S-100 protein (C) and basal cell cytokeratin (D) confirm its identity.

TABLE 2. PIN Voting Results

Statement	% Agree
Low-grade PIN should not be reported in any prostate specimen.	**97%**
It is not necessary to report HGPIN in a radical prostatectomy specimen.	**81%**
It is not necessary to report HGPIN in cases with prostate cancer or contiguous ASAP.	**77%**
Morphologic HGPIN with a cribriform pattern in prostatic biopsies should be reported as AIP.	**75%**
Although its clinical and biologic significance is uncertain, multifocal (≥ 2 biopsy sites) high-grade PIN should be reported in biopsy sets lacking prostate cancer.	**93%**

Bold indicates a consensus.

papillary architecture showing either marked nuclear atypia (in some studies, with nuclei $>6\times$ normal size, (Fig 1H) or necrosis are sufficient for an IDC diagnosis.[9,85] This variability in IDC definitions has likely contributed to problems with interobserver reproducibility, particularly revolving around the degree of nuclear enlargement.[86] A 2014 study of 39 experts assessing digital images, 70% overall agreement with HGPIN, 43% with IDC, and 73% with invasive carcinoma. Respondents considered 19 (50%) of 38 cases as IDC candidates, of which 5 of 19 images (26%) had a two-thirds consensus for IDC; although 9 (47%) reached two-thirds consensus for either AIP or IDC. (A limitation of the study was that observers did not assess whole slides.)

IDC is reportedly associated with cancer that is high grade, high stage, and high volume.[9,84,85] IDC has also been associated with adverse prognostic factors and biochemical or clinical recurrence.[54,87] IDC is most frequently seen concomitant with high-grade invasive prostate cancer. This may be interpreted in 2 ways: either that IDC is a lesion late in the disease course, following the emergence of invasive cancer (prevailing view), or that IDC evolves in parallel with invasive carcinoma. However, isolated IDC without adjacent cancer has only very rarely been identified, more distinctly calling into question IDC as a precursor. The major differential diagnostic considerations for IDC are AIP (see below), invasive cribriform carcinoma, which lacks basal cells, cribriform basal cell hyperplasia, clear cell cribriform hyperplasia, and prostatic ductal adenocarcinoma.[9] The latter relies on pseudostratified columnar cells, arranged in papillary/cribriform architecture with slit-like lumens, that may be either invasive or grow in ducts.

Molecular Findings

Several molecular findings have been reported for IDC. Copy number alterations are common, including higher rates of loss of heterozygosity (LOH) at certain microsatellite markers than for invasive pattern 4 cancer,[88] and several chromosomal imbalances when compared with HGPIN.[89] More recently, studies have focused on *PTEN* and *ERG*. As *PTEN* loss usually occurs in cases with ERG rearrangement, these 2 markers may be used to assess clonality and temporal relationships in prostate carcinogenesis. The percentage of IDC with partial or complete *PTEN* loss by immunostaining has been reported as 58% to 84%,[87,90,91] (this is higher than for the average for invasive cancer—which varies by grade), while many IDC cases with *PTEN* loss also have *ETS* gene rearrangement. The rate of *ERG* rearrangement in IDC has been variously reported as ranging from 55% to 75%,[87,89,90,92] and was concordant with the status of accompanying invasive cancer.[92]

As previously noted, it is rare for IDC to occur as an isolated finding (no invasive cancer) at prostatectomy or with only grade group 1 cancer. Such lesions are less likely to have *PTEN* loss (47% vs. 69% to 84% for IDC with invasive cancer) and rarely harbor *ERG* rearrangement (7% vs. 55%-75% for IDC with invasive cancer). A study of 15 such lesions[93] with next-generation sequencing discovered activating oncogenic driver mutations in MAPK and PI3K pathway genes in isolated IDC, which were not seen in accompanying grade group 1 invasive cancer. These findings support the notion of IDC as a separate high-grade and likely preinvasive lesion in such cases instead of as a precursor to the low-grade invasive cancer.

The temporal relationship between HGPIN, IDC, and invasive carcinoma remains controversial in large part because it has been difficult to study this question by longitudinal analysis. Using *ERG* expression status and *TMPRSS2-ERG* genomic breakpoints as markers of clonality, and *PTEN* deletion status for tracking the temporal evolution of clonally related lesions, Haffner et al[94] showed by whole genome sequencing that IDC was clonally related to its nearby invasive cancer. Specifically, they found that a significant fraction of ERG-positive, PTEN-negative HGPIN and IDC lesions were most likely clonally derived from adjacent PTEN-negative invasive adenocarcinomas. This would indicate that over half of IDC (and at times even some HGPIN) lesions with *PTEN* loss are not cancer precursors but rather, arise from retrograde spread of nearby invasive carcinoma into normal duct-acinar spaces (akin to an *in situ* lesion of the breast). Further support for the retrograde spread hypothesis was offered by another study showing that bilateral lymph node metastases were more molecularly similar to areas of IDC than they were to invasive tumor in the primary specimen, suggesting that ductal colonization occurs concomitant with the acquisition of metastatic ability.[95]

A subsequent microdissection/whole genome sequencing study, however, suggested that IDC's genetic alterations fit neither as a pure precursor of invasive carcinoma nor as a pure progression phenomenon from invasive cancer.[96] For example, whenever both IDC and invasive components coexisted, in some instances *MED12L* gain occurred only in the invasive component, and in some instances *MYC* amplification was exclusively

in IDC or in invasive cancer. This indicates that the spatial and molecular relationship between IDC and adjacent invasive carcinoma is complex and may vary depending upon individual lesions studied. This study also demonstrated that among germline BRCA2-mutant cancers, there is an association with IDC. In the *Wnt* pathway, *MED12L*/*MED12* amplification is more common in germline BRCA2-mutant cancers, and again, is enriched in IDC.[96] Finally, IDC was common in the TCGA molecular subset of *SPOP* mutant cancers,[97] and IDC possesses high rates of *TP53* and *RB1* mutation.[92]

Practical Perspective on IDC

In prostatic needle biopsy, isolated IDC or IDC occurring with grade group 1 cancer generally indicates the presence of unsampled high-grade cancer. This should certainly prompt repeat sampling, and many have suggested that it should preclude active surveillance.[85,98] Whether or not to include accompanying IDC in the grading of invasive carcinoma was deliberately not addressed at this meeting, since this did not relate to IDC as a precursor. The repetitive emphasis in the literature placed on discrepant ISUP versus GUPS recommendations about IDC incorporation into the grade, has engendered confusion;[99] as a practical matter, the volume of IDC in a specimen is rarely enough to change the grade group.[100] The 2 societies held a joint meeting in Boston (March 2025) to present and debate matters focused exclusively on IDC. The voting process among its attendees is still pending as of this writing. This will result in a separate Boston publication that will address the most important issue: the grading of IDC. The Florence meeting did not address this critical issue regarding the grading of IDC, in which ISUP and GUPS had different recommendations.

Consensus Voting

Notably, conference participants who voted indicated that dense expansile cribriform to solid architecture was a stronger criterion for IDC diagnosis than extreme nuclear enlargement alone—82% versus 65% (Table 3). This is in line with the above findings of a reproducibility study,[101] and with data about nuclear enlargement.[86]

Atypical Intraductal Proliferation

Atypical intraductal proliferation (AIP), which has also been termed atypical cribriform lesion (ACL) or atypical proliferation suspicious for intraductal carcinoma (ASID)[91,102] is currently defined as showing "a greater degree of architectural complexity and/or cytologic atypia" than HGPIN but falling short of the criteria for IDC.[98] Hickman et al posited that AIP has "(1) a lumen-spanning loose cribriform pattern and (2) relatively uniform nuclei that lack the nuclear features characteristic of classic IDC and a lack of intraluminal necrosis."[87] Nonetheless, not all authors would require a lumen-spanning proliferation. Loose cribriform has been defined as having luminal spaces accounting for $>50\%$ of an intraductal cellular mass proliferation.[103]

Two different examples of AIP are illustrated, with the first having greater cellularity (Fig. 1I) and the second having less cellularity but greater nuclear atypia (Fig. 1J).

Molecular Findings

The rate of *ERG* positivity in AIP varies widely among reports (27% to 72%).[87,90–92,104] However, there has been nearly 100% concordance in *ERG* positivity between AIP and invasive cancer in 2 studies that examined this,[90,91] suggesting a shared clonal origin. Regarding *PTEN* loss, a 52% to 100% rate has been reported,[73,87,90–92,104] which is certainly higher than that of HGPIN (0%) and closer to that of IDC. The rate of concordance of AIP *PTEN* loss with the invasive component was again quite high (77% to 100%) in 3 studies that examined it.[87,90,91] The wide variance in these molecular alteration frequencies in AIP further reinforces the idea that AIP—like ASAP—represents a rather wide diagnostic category of lesions, rather than a uniformly distinct biological entity. This also indicates that much additional study is needed on AIP, including cases with clinical follow-up and molecular features. Interestingly, recently, a biomarker panel (Appl1/Sortilin/Syndecan-1) was proposed to help overcome diagnostic uncertainty surrounding AIP and sort it into HGPIN or IDC[8]; however, this marker panel still needs corroboration and molecular correlation.

Practical Perspective on AIP

True isolated AIP can be diagnosed with certainty only in fully embedded prostatectomy tissue. Isolated AIP in biopsies is rare, since most instances have accompanying cancer. Only 2 follow-up studies exist tracking repeat biopsies, both showing that isolated AIP predicted a subsequent diagnosis of cancer in 50%-67%, far higher than for HGPIN. Shah et al[103] reported 12 AIP-only

TABLE 3. IDC Voting Results

Statement	% Agree
IDC is a cytologically malignant epithelial proliferation, usually in a dense cribriform pattern, filling and distending large acini and prostatic ducts, with at least focally preserved basal cells.	**98%**
In the absence of a dense cribriform to solid proliferation, marked nuclear enlargement and pleomorphism (beyond that of high-grade PIN) alone may be sufficient to diagnose IDC.	65%
In the absence of marked nuclear enlargement and pleomorphism (eg, beyond that of high-grade PIN), a dense cribriform to solid proliferation may still be diagnosed as IDC (as distinct from AIP).	**82%**
Research suggests that IDC most often represents retrograde gland/duct colonization.	**94%**

Bold indicates a consensus.

patients. Among the 6 who underwent repeat biopsy, 4 had cancer of varying grades, 1 accompanied by IDC. The second study was of 36 AIP-only patients who underwent repeat biopsy: 18 (50%) had a malignancy, 15 with invasive cancer, and 3 with IDC-only.[104]

A recent study correlated AIP biopsy findings (n = 126) with outcome, including 47 men who underwent prostatectomy and had available slides to review.[105] The study group had grade group 1 to 2 cancer with AIP (no IDC or cribriform tumor) on biopsy, and a control group had the same without AIP. Unfavorable histology at prostatectomy was noted in 89% of the study group but only 38% of the control group. Neither the PTEN nor the ERG immunostain results of the AIP focus were significantly predictive of prostatectomy findings. This suggests that the risk of AIP for unsampled high-risk prostate cancer warrants its reporting in grade group 1 or 2 biopsies, where patients may be active surveillance candidates.

In a study solely based on radical prostatectomy findings, 46 of 310 cases had AIP or IDC associated with an invasive cancer. AIP-associated (n = 10) and/or IDC-associated (n = 36) carcinoma showed a higher stage and grade compared to acinar carcinoma without these features (n = 264, $P < 0.01$). AIP-associated and IDC-associated carcinomas did not differ from each other in stage, grade, positive lymph nodes, or PTEN/ERG status.[87] In a prostatectomy study with clinical follow-up, among 901 cases with either IDC, AIP, or HGPIN,[54] cases with AIP showed a significantly higher risk of biochemical recurrence than those with HGPIN but significantly lower risk than those with IDC by univariate analysis only. Cases with AIP also showed significantly higher Gleason score, larger tumor volume, and more advanced pT stage than those with HGPIN. Taken together, these findings suggest that the clinically relevant characteristics of AIP are more similar to IDC than to isolated HGPIN.

Consensus Voting

In the premeeting survey, 67% of respondents stated they would perform a triple (PIN4 cocktail) stain if AIP alone were detected in a case and would include a comment regarding its clinical implication. This effort to exclude invasion is justified since invasive pattern 4 adenocarcinoma with cribriform features may mimic AIP. Likewise, for AIP detected together with grade group 1 invasive carcinoma, 75% would confirm it by immunostaining, which also would exclude the possibility of an invasive pattern 4 cancer. This is in line with the WHO recommendation that AIP on needle biopsy warrants early repeat biopsy.[9] Most respondents would not add an immunohistochemical stain for AIP, accompanied by higher grade cancer.

At the meeting (Table 4), a consensus was easily reached on questions 1 and 3: on a lesion type that should be diagnosed as AIP, and on the need for an explanatory note in needle biopsies containing either AIP alone or along with grade group 1 cancer. Indeed, AIP has strong predictive value for more clinically significant cancers. Conversely, in radical prostatectomy specimens, only 19% of voting participants would report AIP, regardless of grade group, given the absence of data on its additive predictive value beyond grade, stage, and margin status in this specimen type.

Atypical Adenomatous Hyperplasia/Adenosis and Proliferative Inflammatory Atrophy

Atypical adenomatous hyperplasia (AAH or adenosis) consists of a circumscribed cluster of crowded small glands with no or minimal nuclear atypia that lack an infiltrative pattern. The most important differential diagnosis for adenosis is Gleason pattern 3 invasive adenocarcinoma (some of which may have been traditionally diagnosed as Gleason pattern 1 or 2). AAH/adenosis is most often located in the transition zone, so it is most common in transurethral resections and is less often sampled on needle biopsies. AAH/adenosis shows at least a discontinuous basal cell layer (Fig. 1K) and often slight to moderate AMACR reactivity on immunohistochemical staining.[66]

The rationale for discussing AAH/adenosis at this meeting was that certain of its molecular genetic and morphologic alterations overlap with carcinoma.[65,66,106,107] FISH studies of adenosis have shown that 60% have loss of chromosome 8p, 9% have alterations in chromosomes 7, 8, 10, 12, and Y, and expression of PTOV1 is elevated, similar to HGPIN. Telomere shortening, a feature of both HGPIN and invasive cancer,[65] has been reported in ~20% of AAH/adenosis, compared with 68% of PIN and 83% of carcinoma. Of note, AAH/adenosis foci with telomere shortening or coexisting adjacent carcinoma more often showed AMACR expression.[66] However, *TMPRSS2-ERG* rearrangement was lacking in 55 AAH/adenosis specimens in one study.[106]

These findings suggest that AAH/adenosis may be a precursor to grade group 1 adenocarcinoma.[65,66,106,107] The value of reporting this finding may be to alert other con-

TABLE 4. AIP Voting Results

Statement	% Agree
An intraductal loose cribriform proliferation with nuclear atypia featuring prominent nucleoli, but lacking dense cribriform/solid architecture, highly pleomorphic nuclei, and/or comedonecrosis, should be diagnosed as "atypical intraductal proliferation."	**93%**
In needle biopsies, report the presence of AIP both when it is an isolated finding and when it is seen accompanied by invasive carcinoma.	59%
AIP that is present in a needle biopsy, either alone or with maximum grade group 1 cancer in a given case, should be accompanied by an explanatory comment.	**83%**
In radical prostatectomy specimens without definite IDC, report the presence of AIP regardless of the grade group of the invasive cancer.	19%

Bold indicates a consensus.

TABLE 5. PIA and AAH/Adenosis Voting Results

Statement	% Agree
It is optional and reasonable to report atrophy or PIA in prostatic biopsies when the lesion in question has features that mimic, or may be considered suspicious for, invasive carcinoma	66%
AAH/adenosis is rarely sampled in prostatic biopsies. It is optional to report AAH/adenosis in biopsies, but it is recommended in cases that appear suspicious for low-grade invasive adenocarcinoma.	54%

Absence of bold indicates no consensus.

sulting pathologists to a focus of interest and explain why it was not diagnosed as cancer. However, it was agreed that this warrants at most inclusion as a comment or microscopic description, rather than as a top-line diagnosis.

Proliferative inflammatory atrophy (PIA) (Fig 1L) describes "discrete foci of proliferative glandular epithelium with the morphological appearance of simple atrophy, or postatrophic hyperplasia, occurring in association with inflammation."[78] PIA has been observed to merge at times with or transition directly to HGPIN.[78,79] PIA foci have an elevated proliferative fraction of cells, shown by higher levels of proliferation marker Ki67.[108] Molecular data have shown slightly greater *GSTP1* methylation in PIA foci than in normal epithelium, but less than in PIN.[78] While most studies have shown a lack of *TMPRSS2-ERG* gene rearrangements in PIA/focal atrophy[70] or only rare occurrences, this gene fusion along with *ERG* mRNA and protein has been observed in PIA lesions occurring in highly inflamed cases where the atrophic epithelium was in transition to early invasive cancer.[109,110] A topographic digital annotation study of inflammatory atrophic lesions in prostatectomy tissue[4] showed that atrophy with inflammation was more likely to be close to cancer foci than atrophy without inflammation ($P = 0.0001$). This suggests at least a weak linkage between PIA and low-grade cancer. Conversely, in biopsies, PIA has been correlated with a decreased risk of clinically significant cancer (odds ratio 0.54).[47] The above findings suggest that PIA may be a precursor to some incipient cancers, or PIN lesions, and this has biologic implications that may be used for cancer prevention. While some atrophic lesions are considered part of the spectrum of PIA, such as postatrophic hyperplasia, may at times mimic invasive adenocarcinoma, this can be ruled out with basal cell and/or PIN4 cocktail) staining, and the routine diagnosis of PIA is not considered clinically useful at present.

Consensus Voting

Participants agreed that AAH/adenosis and PIA lack actionable implications for contemporary clinical practice (Table 5). Consensus was not reached for reporting either.

CONCLUSIONS

Our knowledge base regarding epithelial lesions associated with prostate cancer development has evolved since 1986. Thus, criteria and terminology used for precursor lesions need to evolve commensurate with their implications for clinical care. The following practice recommendations emerged from the ISUP 2024 consensus meeting, supported by literature and expertise of both pathology and clinical colleagues:

(1) Do not report low-grade PIN
(2) HGPIN need not be reported in the presence of concomitant cancer or atypical small acinar proliferation suspicious for tumor
(3) For IDC, a dense cribriform to solid proliferation without marked nuclear atypia and pleomorphism is a stronger criterion than extreme nuclear atypia and pleomorphism, although both are often present
(4) Cribriform HGPIN should be redesignated as AIP
(5) AIP alone or seen together with grade group 1 cancer warrants an explanatory comment because of its association with adverse features; AIP that is in the presence of invasive cancer need not be reported
(6) PIA and AAH/adenosis are not necessary to report (but at the pathologist's discretion might be included in a microscopic description)

The above guidelines should help the practicing pathologist to maximize their attention to observe and report findings that are clinically actionable and avoid reporting findings that are noncontributory to patient care. Standardization should make pathologists' reporting of prostate precursor lesion findings more consistent.

ACKNOWLEDGMENTS

The authors thank all the respondents to the ISUP membership survey.

Other Members of ISUP GU Cancer Precursor Consensus Panel:

Andres Acosta (USA), Adebowale Adeniran (USA), Nabil Adra (USA), Mahmut Akgul (USA), Hikmat Al-Ahmadie (USA), Ferran Algaba (Spain), Yves Allory (France), Khaleel Al-Obaidy (USA), Mahul Amin (USA), Georgios Andreou (Sweden), Marc Barry (USA), Dilek Baydar (Turkey), Stephania Bezerra (Brazil), Felix Bremmer (Germany), James Brugarolas (USA), Matteo Brunelli (Italy), Lukas Bubendorf (Switzerland), Katie Buzacott (Australia), Birgitte Carlsen (Norway), Alcides Chaux (Paraguay), Fei Chen (USA), Roselyne Choiniere (the Netherlands), Maurizio Colecchia (Italy), Katrina Collins (USA), Eva Comperat (Austria), Roberto Contieri (Italy), Michael Cookson (USA), Antonio Cubilla (Paraguay), Francesca D'Souza (Australia), Alis Dema (Romania), Gedske Daugaard (Denmark), Regina de Paula Xavier Gomes (Brazil), Klaus-Peter Dieckmann (Germany), Dejan Dobi (USA), Michelle Downes (Canada), Andrew Erickson (Finland), Bishoy Faltas (USA), Alexander Fichhtner (Germany), Achim Fleischmann (Switzerland), Jacqueline Fontugne (France), Rongbin Ge (USA), Giovanna Giannico (USA), Timothy Gilligan (USA), Jennifer Gordetsky (USA), Raluca Grigorescu (United Kingdom), Rainer Grobholz (Switzerland),

Charles Guo (USA), Sounak Gupta (USA), Lavinia Hallam (Australia), Ari Hakimi (USA), Donna Hansel (USA), Arndt Hartmann (Germany), Loren Herrera Hernandez (USA), Rafael Jimenez (USA), Merce Jorda (USA), Ashish Kamat (USA), Payal Kapur (USA), Seema Kaushal (India), James Kench (Australia), Margaret Knowles (United Kingdom), Li Lei (USA), Subodh Lele (USA), João Lobo (Portugal), Leendert Looijenga (the Netherlands), Antonio Lopez-Beltran (Spain), Anand Loya (Denmark), Fiona Maclean (Australia), Alopa Malaviya (United Kingdom), Guido Martignoni (Italy), Rohit Mehra (USA), Santosh Menon (USA), Laura Mertens (the Netherlands), Holger Moch (Switzerland), Sambit Mohanty (India), Helmut Mühleisen (Germany), Andrea Necchi (Italy), Ngoc-Nhu Jennifer Nguyen (USA), Maya Nourieh (France), Mikko Nyman (Finland), Pedro Oliveira (United Kingdom), Declan O'Rourke (United Kingdom), Gladell Paner (USA), Ewa Rajpert-De Meyts (Denmark), Maria Raspollini (Italy), Sigrid Regauer (Austria), Henning Reis (Germany), Ohashi Riuko (Switzerland), Antonio Rodriguez-Calero (Switzerland), Jeffrey Ross (USA), Diego Sanchez (Paraguay), Ankur Sangoi (USA), Fanni Sánta (USA), Steven Shen (USA), Brian Shuch (USA), Steven Smith (Croatia), Philippe Spiess (USA), John Srigley (Canada), Yue Sun (USA), Sueli Suzigan (Brazil), Nicole Swarbrick (Australia), Pheroze Tamboli (USA), Puay Hoon Tan (Singapore), Zahrah Tawil (Malaysia), Satish Tickoo (USA), Maria Tretiakova (USA), Isabel Trias (Spain), Lawrence True (USA), Toyonori Tsuzuki (Japan), Monika Ulamec (Croatia), Theodorus Van der Kwast (Canada), Bas van Rhijn (the Netherlands), Funda Vakar Lopez (USA), Elsa Velazquez (USA), Mariavittoria Vescovo (Italy), Gang Wang (Canada), Anne Warren (United Kingdom), Joshua Warrick (USA), Sean Williamson (USA), Sara Wobker (USA), Chin-Lee Wu (France), Huihui Ye (USA), Xiaolin Zi (USA), Hong Zhang (USA).

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