

Amsterdam UMC

International Society of Urological Pathology (ISUP) Multidisciplinary Consensus on Premalignant and Putative Precursor Lesions of Penile Cancer

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Published in:
American journal of surgical pathology

DOI:
[10.1097/PAS.0000000000002453](https://doi.org/10.1097/PAS.0000000000002453)

E-pub ahead of print: 01/01/2025

Document Version
Publisher's PDF, also known as Version of record

Document license
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Citation for published version (APA):

Menon, S., Sanchez, D. F., Chaux, A., Giannico, G. A., Oliveira, P., Necchi, A., Regauer, S., Speiss, P. E., Tamboli, P., Tsuzuki, T., Elsa F, V., Kristiansen, G., Cheng, L., Cubilla, A., & ISUP GU Cancer Precursor Panel (2025). International Society of Urological Pathology (ISUP) Multidisciplinary Consensus on Premalignant and Putative Precursor Lesions of Penile Cancer: Working Group 5 report on Terminology, Grading, and Molecular Testing Practices. *American journal of surgical pathology*, Article 10.1097/PAS.0000000000002453. Advance online publication. <https://doi.org/10.1097/PAS.0000000000002453>

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International Society of Urological Pathology (ISUP) Multidisciplinary Consensus on Premalignant and Putative Precursor Lesions of Penile Cancer

Working Group 5 report on Terminology, Grading, and Molecular Testing Practices

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Abstract: The classification and diagnosis of penile intra-epithelial neoplasia (PeIN) remains inconsistent among pathologists, despite its recognized role and understanding as a precursor to penile squamous cell carcinoma (PSCC). The International Society of Urological Pathology (ISUP) convened a consensus group of multidisciplinary thought leaders to assess current global practices regarding the usage of terminology, grading, and molecular testing in penile cancer precursor lesions. A preconference survey was distributed to ISUP members in 2024, collecting responses from 112 pathologists, predominantly genitourinary specialists, to evaluate the use of penile cancer precursor lesion classification systems, grading approaches, and diagnostic biomarkers. The results were presented at the ISUP Multidisciplinary Consensus Conference on Cancer Precursor Lesions in September 2024, where further consensus was achieved through electronic voting. The survey revealed that 89.4% of respondents classify PeIN based on HPV association, with 76% supporting further subtyping into basaloid, warty, and differentiated subtypes.

Grading of PeIN remains controversial; 51.3% initially favored grading, but 82% finally voted that PeIN should not be graded. p16 immunohistochemistry (IHC) was widely utilized (91.5%) to distinguish HPV-associated from HPV-independent PeIN, whereas p53 IHC and HPV genotyping lacked consensus for routine use. Reporting practices for PeIN margins and their association with lichen sclerosis were widely endorsed, while the value and concordance of subtyping HPV-independent PeIN remains an area for further investigation. This ISUP consensus paper guides PeIN classification, confirming the importance of HPV-related stratification and p16 IHC staining and reporting as standard practice. However, significant variability persists in PeIN grading and molecular testing strategies. These findings highlight the need for further research and standardization to optimize diagnostic accuracy and clinical relevance in PeIN.

Key Words: consensus, human papillomavirus, penile, precursor
(*Am J Surg Pathol* 2025;00:000–000)

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The raw data about this manuscript and the survey results are being submitted as Supplemental File 1, Supplemental Digital Content 1, <http://links.lww.com/PAS/C155>.

This is a survey-based manuscript in which data related to the practice patterns among pathologists, regarding terminology and ancillary tests for rare penile cancer precursor lesions, are presented. There are no issues with patient confidentiality in this manuscript.

Conflicts of Interest and Source of Funding: The authors have disclosed that they have no significant relationships with, or financial interest in, any commercial companies pertaining to this article.

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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.

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DOI: 10.1097/PAS.0000000000002453

There is a bimodal carcinogenetic pathway in penile squamous cell carcinoma, and there are special subtypes reported with or without the human papillomavirus (HPV), harboring distinctive morphologic and clinical features.^{1–3} These findings led the WHO and others to recognize the diversity of penile cancer and to classify it as HPV-associated and HPV-independent. Penile intraepithelial neoplasia (PeIN), the recommended term and putative precursor of invasive penile squamous cell carcinomas, is also classified on similar lines to HPV. About 2% of PeIN lesions are likely to progress to squamous cell carcinoma without treatment.^{4–8} PeIN is often associated with skin disorders afflicting the glans and foreskin, such as lichen planus, balanoposthitis, lichen sclerosus (balanitis xerotica obliterans), as well as immunosuppression related to post-organ transplantation.^{7–10}

Most human papillomavirus (HPV)-independent penile squamous cell carcinomas (PSCCs) originate from the precursor lesion described as differentiated PeIN, which at low power is characterized by atypia limited to the basal layer or lower levels of squamous epithelium with apparent superficial maturation and sometimes verrucous histology. At higher power, however, a very subtle abnormal maturation in all levels of the epidermis and parakeratosis can often be appreciated. HPV-associated penile squamous carcinomas arise from HPV-associated precursor lesions, which are predominantly either basaloid or warty.¹¹ As these are rare lesions/tumors, the experience of pathologists is limited. There is considerable variation in the recognition and terminology applied to these precursor lesions, even among genitourinary pathologists. Moreover, the literature remains controversial regarding their grading, the utility of p16/HPV testing, and reporting preferences. The current article describes the practice patterns among GU pathologists worldwide and aims to establish a consensus on these contentious issues.^{9,12–14}

METHODS

In preparation for the ISUP Multidisciplinary Consensus Conference on Cancer Precursor Lesions of the Genitourinary Organs, Working Group 5 (WG5) on Precursor Lesions of the Penis, collated a survey and circulated it in the summer of 2024 to the ISUP membership (Supplemental File 1, Supplemental Digital Content 1, <http://links.lww.com/PAS/C155>).

The Chair of the ISUP consensus conference and the chairs of WG5 on precursor lesions of the penis convened in an online meeting to prepare a survey with the following aims:

1. Assess the usage of terminologies and classifications used by uropathologists in addressing penile cancer precursor lesions.
2. Gain insights on the current practice of grading penile cancer precursor lesions and their utility.
3. Evaluate practice patterns in assessing HPV status with p16 and molecular testing in penile cancer precursors.
4. Assess practice patterns in reporting penile cancer precursor lesions.

Based on this online meeting, the Chairs of WG5 and the Chair of ISUP prepared an online survey with the aid of the SurveyMonkey portal.

The working group reviewed, discussed, and collated the voting results of the ISUP survey that were subsequently presented on September 12, 2024, at the Multidisciplinary Consensus Conference on Cancer Precursor Lesions of the Genitourinary Organs Consensus (Table 1). The survey responses were analysed, and consensus on a question/practice statement was met when at least 65% of the votes agreed. Based on the survey responses, the members of WG5 reframed the questions where consensus was not reached (Table 2) for discussion at the conference. These dichotomic reframed questions were put forth to the meeting participants for electronic voting again, and data was collated to check for consensus on contentious issues using similar thresholding.

RESULTS

The preconference survey, prepared by members of working group 5 of this ISUP consensus group, was circulated to the ISUP members and received 112 responses on most of the posed questions (Supplemental File 1, Supplemental Digital Content 1, <http://links.lww.com/PAS/C155>). The demographics showed that 74% of the respondents were affiliated with academic centers. Classical light microscopy was in use by 75% of respondents, while 10% commented about being completely transitioned to digital slides.

The respondents were largely GU specialists (87%), while ~9% were general pathologists. Most respondents (48%) handle 5 to 20 penile cancer-related resections annually.

Table 1 summarizes the questions related to PeIN, its terminology, IHC, molecular testing, and grading, the choice of responses, and the percentage of votes per response.

This survey captured the reporting practices and perceptions among expert GU pathologists regarding penile precursor lesions. Figures 1 and 2 highlight some of the responses that reached consensus and some that did not achieve consensus, respectively. Figures 3–7 are some representative images of various penile precursor lesions along with their ancillary IHC. The key findings of the survey are outlined, analysed and presented below.

Objective 1. Terminologies and Classification

In the preconsensus meeting survey, HPV-associated/independent penile intraepithelial neoplasia (PeIN) was the most favored (43.36%) terminology, followed by “PeIN” alone (39.8%) for labeling the penile precursor/precancerous lesions. Historical terms like “Erythroplasia of Queyrat” or “Bowen disease” are no longer used. A significant majority (89.4%) classify penile precursor lesions into HPV-associated and independent categories. Further, the responses show that subtyping of PeIN was done by a notable proportion of reporting pathologists, with around 38% of them further subtyping the PeIN into basaloid, warty, warty-basaloid, and differentiated sub-

TABLE 1. Voting Results for Questions Related to Penile Cancer Precursor Lesions From the ISUP Consensus Conference on Premalignant/Precursor Lesions in the Genitourinary System

Sr. No.	Voting Question	Response	Percentage
1	What is your microscopic workflow?	Classical light microscopy with glass slides Fully digital with scanned slides Others (please specify)	75 10 14.5
2	How many penile resections do you see in your practice?	< 5 resections per year 5-20 resections per year 20-40 resections per year > 40 resections per year	31.5 48.2 14.9 5.2
3	Which is best choice of terminology which you use for penile precancerous lesions?	Penile intraepithelial neoplasia (PeIN) HPV-associated PeIN/HPV independent PeIN Penile intraepithelial neoplasia (low or high grade PeIN) Squamous intraepithelial lesion (SIL) Erythroplasia of Queyrat Bowen disease Squamous cell carcinoma in situ Other (please specify)	39.8 43.3 6.1 3.5 0 0 5.3 1.7
4	Do you classify penile precancerous lesions into HPV-associated and HPV-independent?	Yes No	89.5 10.5
5	Do you subtype penile precancerous lesions as follows? Mark all preferred term you use.	Basaloid Warty Warty-basaloid Differentiated Pagetoid Clear cell All of the above I don't subtype further than HPV-associated/independent I only report PeIN without subtypes	38.9 38 26.5 30.1 10.6 9.7 38 24.7 7.9
6	Do you subtype Differentiated Penile Intraepithelial Neoplasia (usual, hyperplasia like, pleomorphic)?	Yes No	27.7 72.3
7	Do you grade penile precancerous lesion?	Yes No	51.4 48.6
8	If yes, which terminology do you use for grading PeIN?	Grade 1, 2, or 3 Low-grade PeIN/high-grade PeIN Low-grade SIL/high-grade SIL HPV associated low/high-grade PeIN HPV associated low/high-grade SIL Label all as high grade in my report Other (please specify)	3.2 45.6 6.5 16.3 2.1 11.9 14.1
9	Do you subtype squamous hyperplasia (flat, papillary, verrucous, etc).	Yes No	45.6 54.4
10	Do you report lichen sclerosis in association with penile precancerous lesions or in invasive carcinomas?	Yes No	85.8 14.2

TABLE 1. (continued)

Sr. No.	Voting Question	Response	Percentage
11	Do you report lichen planus or lichenoid dermatosis in association with penile precancerous lesions or invasive carcinomas:	Yes No	57.5 42.5
12	Do you report the site of lichen sclerosus associated with neoplasia?	Separate from PeIN Within PeIN Within invasive cancer All of the above None of the above	12.5 1.8 0.8 37.5 47.3
13	Do you subtype lichen sclerosus	Lichenoid In band or classic Lymphocytic depleted All of the above None of the above	2.6 0.9 0.9 13.3 82.1
14	Are you consistently using p16 or other HPV detection techniques to classify HPV associated from HPV independent precursor lesions in your clinical practice?	Yes No Only in doubtful morphology	84 6.3 9.7
15	If you say yes to the question above, which is the test you use in your practice (mark all tests you use)	p16 IHC HPV IHC HPV detection by in situ hybridization assay HPV detection by in situ hybridization HPV detection by PCR based test Other (please specify)	91.5 8.4 21.7 17.9 18.8 4.7
16	What would you label as p16 positive IHC to diagnose an HPV associated precursor lesion? (mark more than one if you need to)	Clusters of 10-20 cells strong nuclear positive Clusters of 10-20 cells strong nuclear and cytoplasmic positive Block nuclear/ cytoplasmic positivity of all dysplastic cells at basal layer with extension upward and sharp demarcation from normal zone of epithelia Basal strong positivity Do you diagnose p16 positivity using the Lower Anogenital Squamous Terminology Standardization Project for HPV-associated lesions: strong and diffuse block staining Other (please specify)	4.4 4.4 67.8 0 18.7 4.4
17	Are you using immunohistochemistry (Ki67, p53 and/ or p16) as an aid in the diagnosis or subtyping of Differentiated PeIN? (mark all test you use)	P16 Ki67 P53 HPV IHQ HPV detection by in situ hybridization assay HPV detection by PCR based test	85.8 53.7 64.1 3.7 18.8 4.7
18	Should HPV independent precursors be subclassified into p53-mutated and p53 wild-type?	Yes No Need more evidence	28.8 7.2 64
19			

TABLE 1. (continued)

Sr. No.	Voting Question	Response	Percentage
20	In a scenario where the precursor PeIN morphology is basaloid but p16 is negative, what's your next step?	Label it as HPV independent PeIN	25
		Label it HPV associated PeIN	1.7
		Resort to HPV testing	68.7
		Label it as mixed PeIN	0
		Other (please specify)	4.4
21	Do you routinely use Ki67 to distinguish Differentiated PeIN from squamous cell hyperplasia?	Yes	27.6
		No	72.7
22	Do you use p53 as aid in the evaluation of penile precancerous lesions?	Yes	56.3
		No	43.7
23	Do you routinely use p16 or other molecular methods for high-risk HPV detection in condylomas?	Yes	51.3
		No	48.7
24	Are you using molecular genotyping for HPV associated penile precancerous lesions:	Yes	30.9
		No	69.1
25	Indicate your preferred method/s for determining HPV genotypes in penile precancerous lesions	In situ hybridization	46.4
		IHC	17.8
		FFPE whole tissue section PCR	18.7
		FFPE laser capture microdissection PCR	3.5
		Genomic profiling	7.1
		Other (please specify)	6.2
26	Should we be diagnosing PeIN in the immediate vicinity/ shoulder area of the main invasive cancerous lesion or should we be interpreting precursor lesions at a little distance say beyond 2 mm away to diagnose PeIN?	Only beyond 2 mm	15.3
		Even just adjacent to invasive cancer	12.6
		Both a and b	41.4
		Not sure	30.6
27	Do you believe grading may be clinically relevant in penile precancerous lesions?	Yes	39.8
		No	18.5
		Need more evidence	31.8
		Not sure	9.7
28	Do you report the presence of penile precancerous lesions in association with invasive carcinomas?	Yes	84.9
		No	15.1
	Do you include margin involvement by PeIN in your reports?	Yes	99.1
		No	0.9

This survey was circulated to the ISUP Membership before the in-person Consensus Meeting held in Florence, Italy.
FFPE indicates formalin-fixed paraffin-embedded; HPV, human papillomavirus; IHC, immunohistochemistry.

TABLE 2. Voting Results From the In-Person Meeting Polling in Florence, Italy, September 2024

Q No.	Question	Response Options	Percentage
Q1	Is HPV associated and HPV independent PeIN terminology the best to classify penile cancer precursor lesions?	Yes	100
		No	0
Q2	Do you subtype penile precancerous lesions?	Yes	76
		No	24
Q3	If you answer “yes” to the previous question, do you subtype HPV associated PeIN into Basaloid/warty/warty-basaloid?	Yes	74
		No	26
Q4	Do you grade penile precancerous lesions?	Yes	25
		No	75
Q5	Should we be grading PeIN?	Yes	18
		No	82
Q6	Is there need to subtype squamous hyperplasia?	Yes	0
		No	100
Q7	Should the site and types of lichen sclerosus be reported?	Yes	21
		No	79
Q8	Should p16 be done on all cases suspected to be PeIN?	Yes	78
		No	23
Q9	Should p53 and ki67 be done on all cases suspected to be HPV independent PeIN?	Yes	58
		No	42
Q10	Should HPV independent precursors be sub-classified into p53-mutated and p53 wild-type?	Yes	60
		No	40
Q11	In a scenario where the precursor PeIN morphology and p16 staining are a mismatch, would you rely and report on morphological features?	Yes	56
		No	44
Q12	In a scenario where the precursor PeIN morphology and p16 staining are a mismatch, would you resort to molecular HPV testing/ ISH?	Yes	77
		No	23
Q13	Should molecular testing for HPV genotyping be done in HPV associated PeIN?	Yes	24
		No	76
Q14	Should HPV PCR be the preferred method for determining HPV genotypes?	Yes	55
		No	45
Q15	Should ISH be the preferred method for determining HPV genotypes?	Yes	50
		No	50
Q16	Should we report PeIN in the immediate vicinity of an invasive penile carcinoma?	Yes	69
		No	31

These polling questions were prepared based on the premeeting survey results (contentious issues and nonconsensus questions were reorganized into polling questions).

types. Almost a quarter of respondents (24.7%) mentioned that they limit their reporting to HPV association/independence without further subtyping. Subtyping differentiated PeIN into hyperplasia-like, usual, and pleomorphic was not done by 72.3% of the participants.

At the proposal and voting during the consensus meeting at Florence, 100% of the respondents agreed that HPV-associated and HPV-independent PeIN terminology is the best approach to classify penile cancer precursor lesions and 76% agreed on subtyping of PeIN/precancerous lesions. There was also consensus on the proposal to subtype HPV-associated PeIN into basaloid, warty/warty basaloid types by 74% of respondents.

Objective 2. Grading of Penile Cancer Precursor Lesions

In the premeeting survey, 51.3% of respondents favored grading PeIN lesions. For those grading PeIN, the preferred terminologies included “low-grade PeIN/high-grade PeIN” (45.6%), with few using LSIL/HSIL terminology (6.5%) and HPV-associated low-grade/high-grade PeIN (16.3%). Clinical relevance of grading was agreed

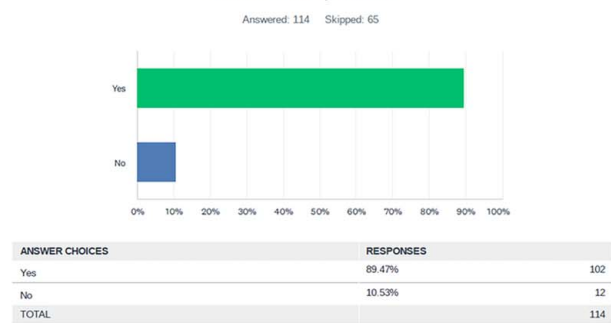
upon by 39.8% while 31.86% opined that the clinical utility of grading needs more evidence.

At the proposal and voting, 82% voted in favor of not grading PeIN, and 75% reported that they do not grade PeIN in their routine practice.

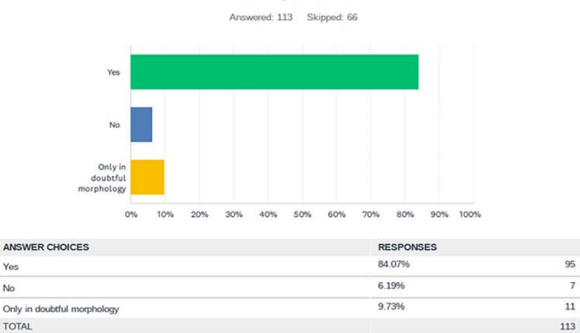
Objective 3. Immunohistochemistry (p16/p53/ki67) and Molecular Testing in Penile Cancer Precursors

In the survey responses, the most used immunohistochemistry test in PeIN was p16 IHC (91.51%), while HPV detection via PCR or ISH is employed by 18% to 22%. The majority (67.86%) define positivity based on diffuse, block nuclear/cytoplasmic staining in all dysplastic cells, sharply demarcated from the normal epithelium. In the case of differentiated PeIN, the use of p16 (85.85%) and p53 (64.15%) was reported in the survey, with Ki67 being employed less frequently (53.7% of respondents). On querying the subclassification of HPV-Independent precursors based on p53, 28.8% supported subclassifying HPV-independent precursors into p53-mutated/wild-type categories, while most (63.9%) agreed that more evidence

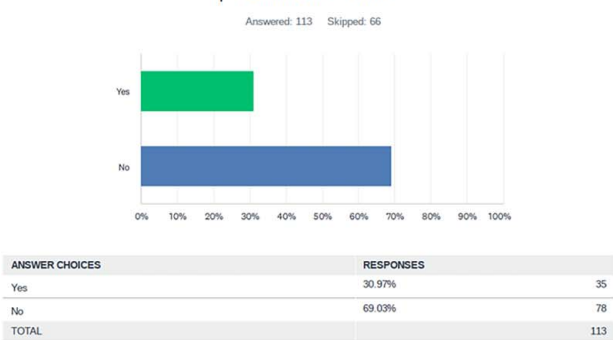
Q119 Do you classify penile precancerous lesions into HPV associated and HPV independent?



Q129 Are you consistently using p16 or other HPV detection techniques to classify HPV associated from HPV independent precursor lesions in your clinical practice?



Q138 Are you using molecular genotyping for HPV associated penile precancerous lesions:



Q143 Do you include margin involvement by PeIN in your reports?

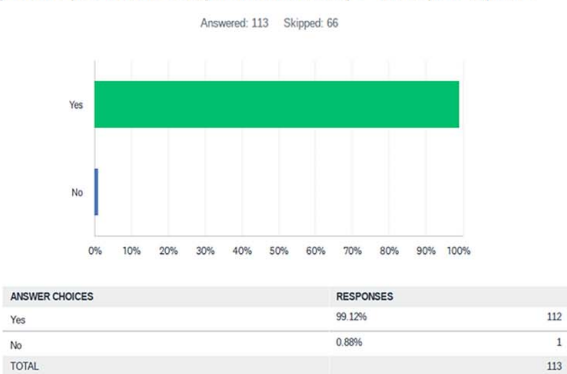


FIGURE 1. Some survey result excerpts from the premeeting survey, which had consensus answers/responses from the respondents (refer to Supplemental File 1, Supplemental Digital Content 1, <http://links.lww.com/PAS/C155>).

is needed. Regarding HPV genotyping, 69% of participants responded negatively to its use in routine practice. For those participants who employed HPV genotyping, the preferred common method was in situ hybridization (46.43%), with PCR and genomic profiling being less common.

At the proposal and voting, 78% agreed to employ p16 IHC in all suspected PeIN cases, whereas routine use of p53 and Ki67 did not reach a consensus among the participants (58%). In cases where morphology is basaloid but p16 is negative, most voted to perform HPV testing (77%) rather than rely on morphologic features (56%). Routine HPV genotyping was not favored by 76% during the final voting. No consensus was reached on whether HPV PCR (55%) testing or HPV ISH (50%) should be used in cases where genotyping ought to be done.

Objective 4. Key Pathology Reporting Points in PeIN

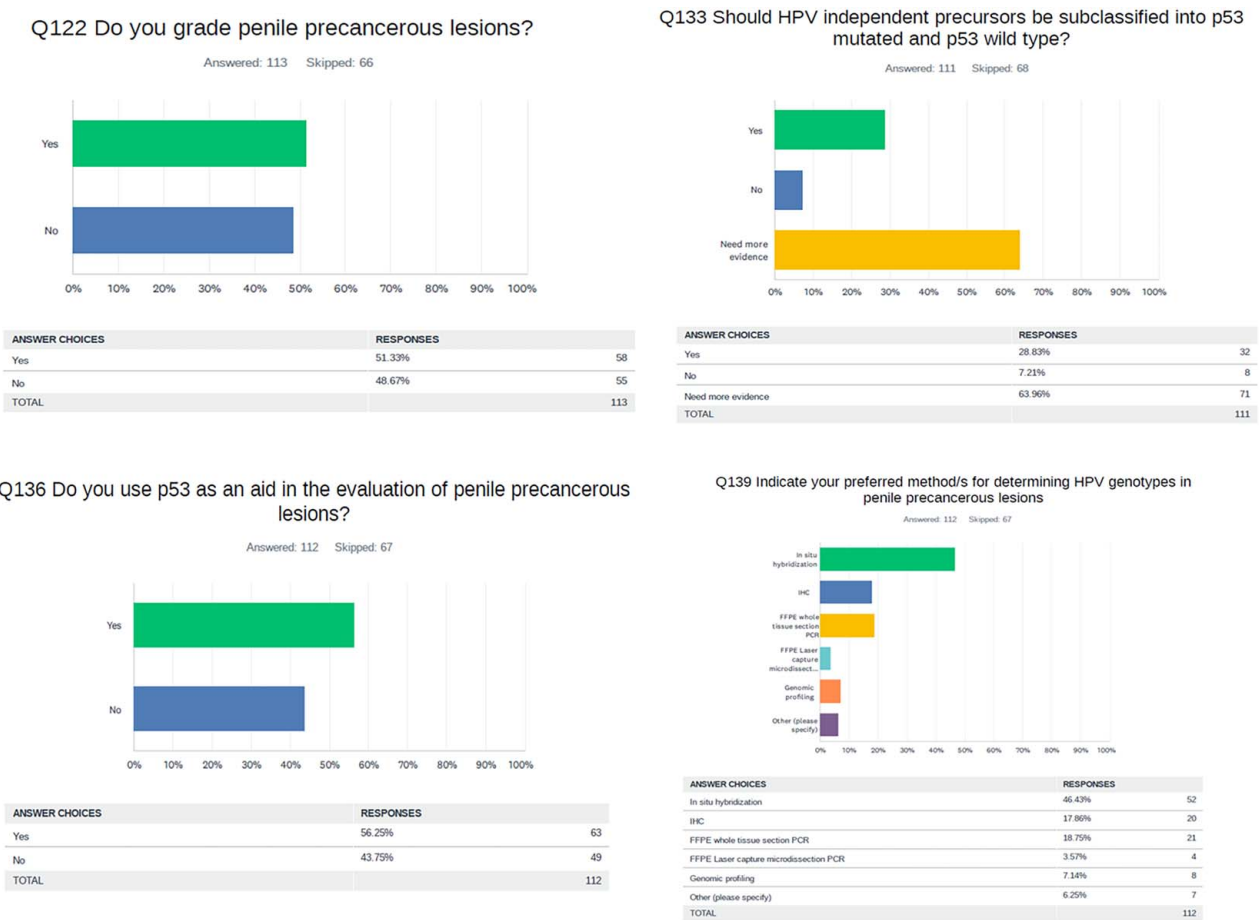
Although classically associated with HPV independent PeIN and invasive cancer, Lichen sclerosis and similar dermatosis may be seen even in HPV associated PeIN/ cancer, as exemplified by the study by Straub Hogan et al.⁷ Also, the spatial correlation of LS may be necessary to document, as we continue to collect data on the association of LS as a possible precursor/precancerous

lesion in penile carcinogenesis.¹⁵ In the pre-meeting survey, 85.71% agreed to report lichen sclerosis in association with PeIN or invasive carcinomas, but there was no consensus (37.5%) on reporting the site of chronic inflammatory dermatosis (lichen sclerosis and lichen planus) in relation to the PeIN/ invasive carcinoma. However, 82.1% agreed that there is no need to subtype lichen sclerosis. Regarding squamous hyperplasia, 54.5% of participants disagreed with further subtyping. The query on whether to include PeIN just adjacent to invasive cancer or beyond a 2 mm focus of invasive cancer did not reach a consensus, with 41.44% agreeing to report PeIN both adjacent to and beyond 2 mm from invasive cancer. Nearly all respondents (99%) include margin involvement by PeIN in their reports.

At the proposal and voting, 79% voted in favor of not specifying the site of lichen sclerosis and a consensus was also reached regarding the reporting of PeIN in the immediate vicinity of invasive squamous carcinoma, with 69% agreeing to the proposal.

DISCUSSION

The understanding of penile cancer precursor lesions has evolved considerably, particularly in terms of their classification and nomenclature, which have been subjects



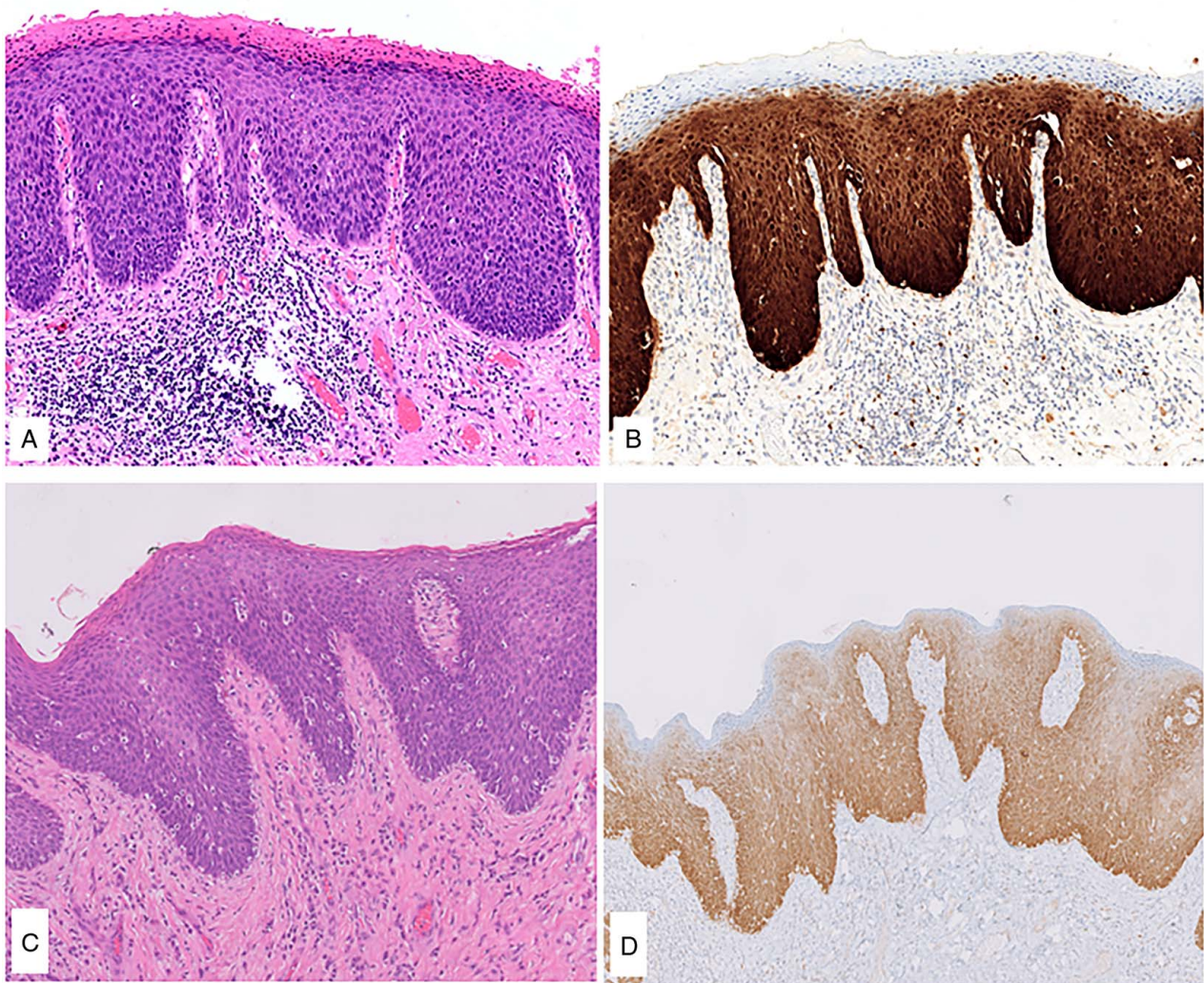


FIGURE 3. HPV-associated PeIN-basaloid PeIN with almost full thickness of squamous epithelium showing small basaloid blue cells (A). Block-like p16 positivity in basaloid PeIN (B). Basaloid PeIN with apoptotic cells (C) and p16 block-like reactivity in it (D).

lichen planus, and squamous hyperplasia, can mimic or coexist with PeIN, leading to diagnostic ambiguity.^{10,13,15} Over the years, all these modifications in nomenclature and classification have contributed to varied practices among pathologists, including specialist uropathologists, and are further compounded by the fact that these lesions are rarely seen in most daily practices. The current survey results reiterate the prevalent usage of this nomenclature and classification, as 89.4% of participants responded to the usage of the HPV-associated and HPV-independent terminology. Only 3.5% and 5.3% of respondents use the SIL terminology and squamous carcinoma in situ term, respectively. At the consensus meeting, 100% of those surveyed agreed to use this nomenclature. There was a clear consensus (74% agreement) on subtyping PeIN, as well as further subtyping of HPV-associated PeIN, into

basaloid, warty, and basaloid-warty, both in the pre-meeting survey as well as at the consensus meeting. A similar consensus, however, was not attained as regards subtyping HPV-independent differentiated PeIN into usual, hyperplasia-like, and pleomorphic, with 72.3% of negative responses.

The grading of PeIN is a controversial issue, as amply highlighted by the premeeting survey responses, with 51.3% of participants agreeing to grading PeIN as opposed to 48.7% disagreeing. It is a widespread phenomenon in pathology practice to grade intraepithelial and preinvasive lesions, as is exemplified in the cervix and vulva organ systems. In penile cases, however, this has remained contentious with no recommended guidelines. The WHO 2022 considers PeIN high grade and, hence, not susceptible to grading.^{5,21} Nonetheless, some cancer

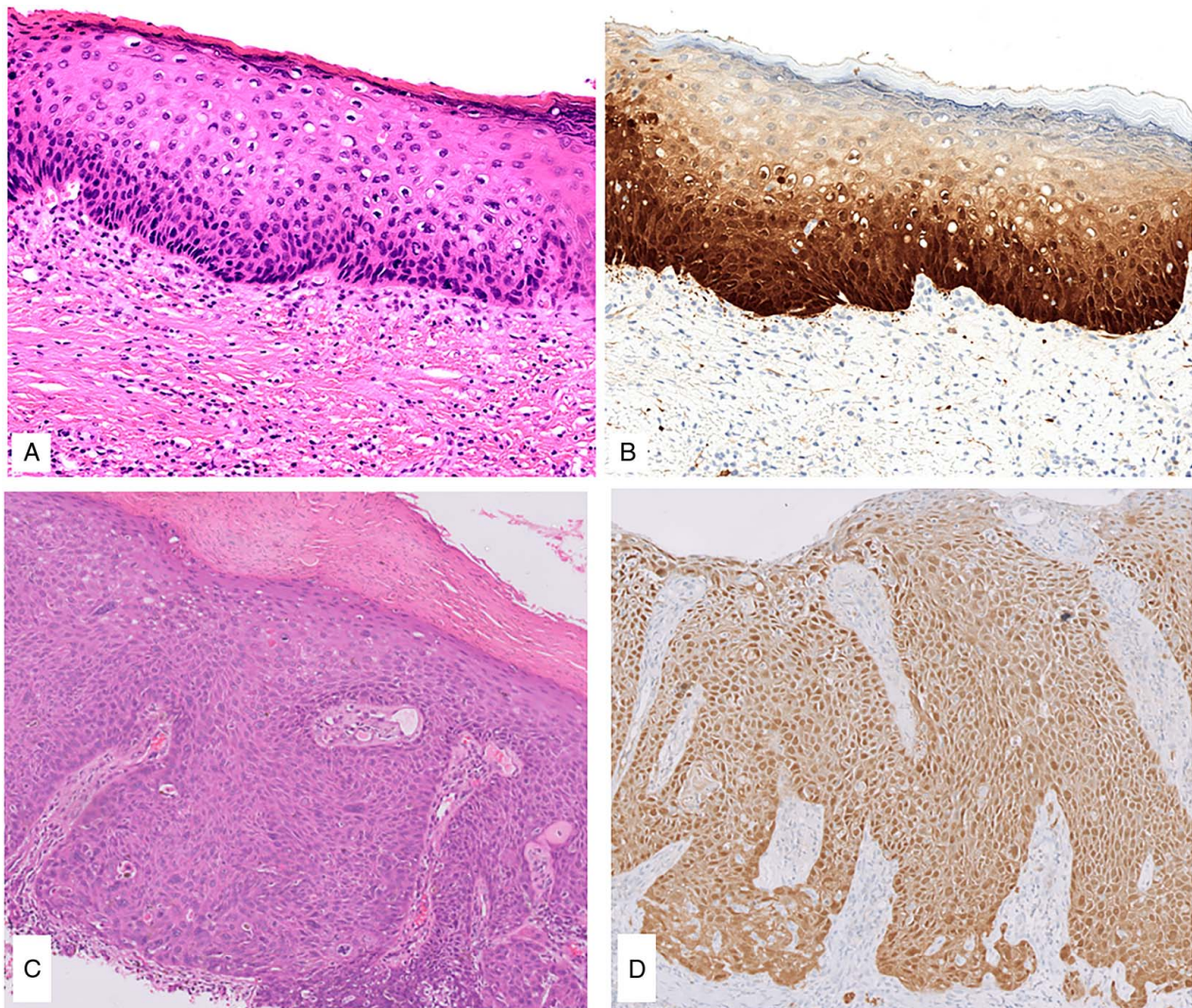


FIGURE 4. HPV-associated PeIN-Warty basaloid PeIN with an upper flat surface showing koilocytosis and lower epithelium showing blue basaloid cells (A). p16 diffuse strong block immunoreactivity in wart basaloid PeIN (B). The basaloid PeIN may be comprised of pleomorphic cells in the epithelium (C), and p16 is necessary to assess the block positivity in such cases (D).

registries and groups of authors mention grading PeIN into low/high grade and PeIN 1/2/3.^{25,26} The distinction between low-grade and high-grade PeIN may be critical for clinical management, as high-grade lesions have a higher risk of progression to invasive carcinoma and may require more aggressive treatment. The use of terms like “carcinoma in situ” can lead to overtreatment, as it may be perceived as more aggressive than “high-grade PeIN.” Conversely, “low-grade PeIN” may be underemphasized, potentially delaying necessary follow-up or intervention.^{9,27} In the current survey, the respondents who grade PeIN use low/high as the preferred terminology (45% usage among those grading PeIN). At the consensus meeting, 75% of the surveyed agreed that they do not grade PeIN in their practice, and 82% agreed that PeIN should not be graded, which is in agreement with the

WHO classification and current understanding.^{4,5,20} Only 39% of the survey participants believed that grading may be clinically relevant, and 31% suggested that “more evidence is needed” to emphasize the clinical utility of PeIN grading. It is reasonable to conclude that the current grading of PeIN is not done in routine practice and that more work needs to be done, with multicentric collaboration, to arrive at a more meaningful and clinically relevant grading.

The widespread usage of p16 IHC in routine practice is well demonstrated by the current survey, with 91% of participants agreeing that they utilize it regularly to classify PeIN into HPV-associated and HPV-independent subtypes. While the utility of p16 is considered in the WHO 2022 classification, only the European Association of Urology and the Royal College of Pathology guidelines

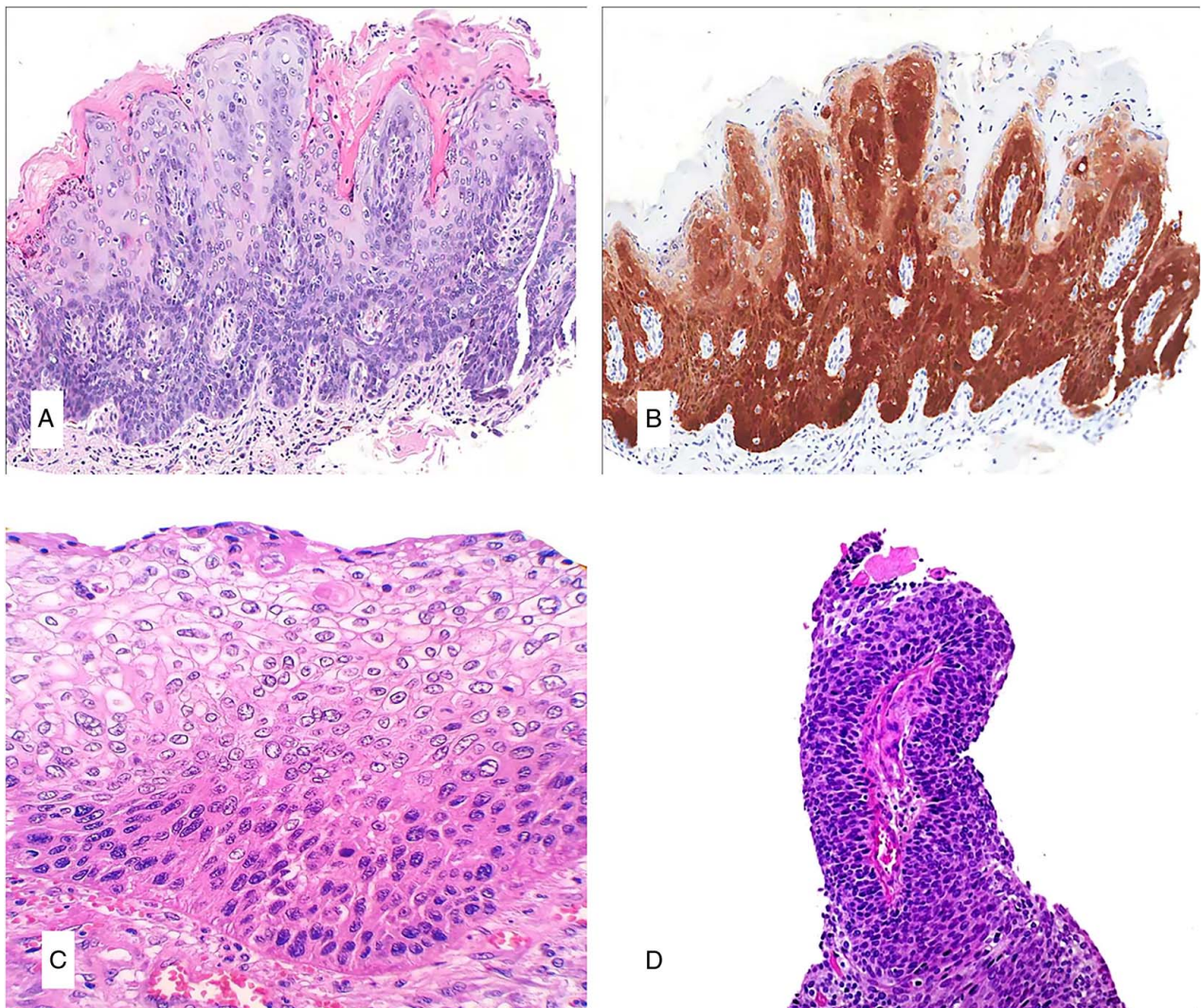


FIGURE 5. HPV-associated PeIN-Warty basaloid PeIN with a pronounced warty surface pattern (A) and p16 positivity (B). Warty basaloid PeIN with a flat warty surface, with koilocytosis and the basal part showing basaloid cells (C). Papillary basaloid PeIN is a rarer pattern (D).

require p16 IHC for PSCC and PeIN classification²⁸ (RCPATH cancer datasets and tissue pathways: <http://www.rcpath.org/profession/guidelines/cancer-datasets-and-tissue-pathways.html>). p16 may be particularly useful in the pleomorphic morphology of HPV independent PeIN, wherein a warty basaloid PeIN with pleomorphic warty cells would be a close differential diagnosis. Similarly, a subtle warty PeIN may resemble an HPV independent PeIN and may need a p16 to resolve the dilemma.^{4,14,29} In the ambiguous scenario of a basaloid PeIN with p16 negativity, there was a vote in favor of utilizing HPV molecular testing/HPV ISH (77% consensus). This is based on the understanding that some basaloid-appearing lesions may be negative on molecular testing.¹¹ It is interesting to note that with the growing understanding of the role of p53 mutation in HPV independent carcinogenesis

pathway, a significant proportion (64%) of participants in the initial survey agreed on the use of p53 immunohistochemistry in differentiated PeIN, although only 29% use the terminology p53 mutated vs wild-type for HPV-independent precursor lesions.^{29,30} Regauer et al,¹³ in their seminal work, have proposed that there are 2 possible biological pathways associated with HPV-independent precursors which include the differentiated PeIN in chronic inflammatory dermatoses, with p53 overexpression and *TP53/CDKN2A* mutations, and the p53 wild-type verrucous/verruciform precursors driven by mutations in oncogenes *PIK3CA* and *HRAS* in the associated verrucous squamous carcinoma.³¹ At the consensus meeting, post discussions, no consensus was obtained for either routine use of p53/Ki67 or for classifying HPV-independent PeIN into p53 mutated versus wild-type (58%

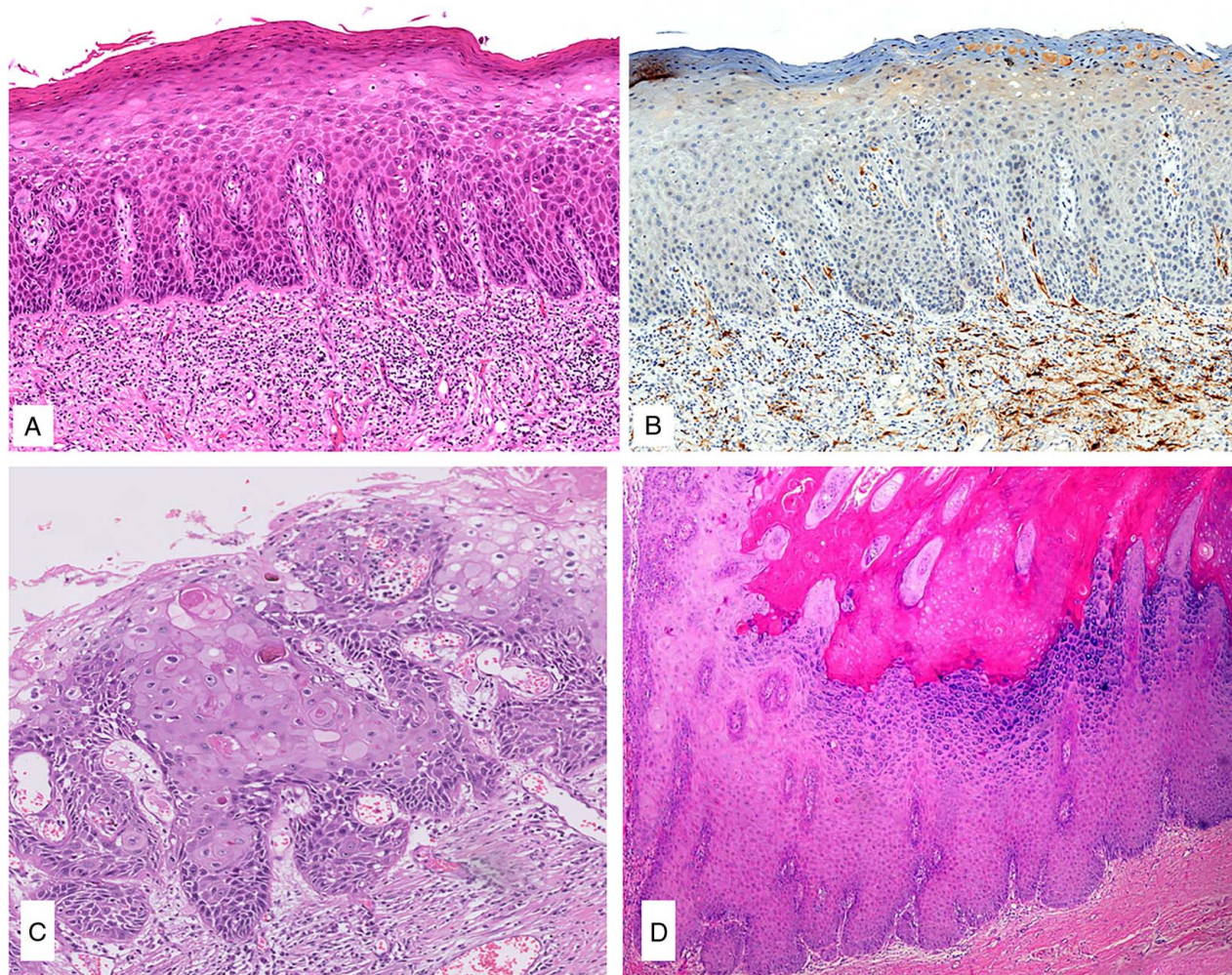


FIGURE 6. HPV independent PeIN-differentiated PeIN with prominent rete ridges and abnormalities of basal/parabasal cells with maturation towards the superficial layer (A) and p16 negativity (B). In some differentiated PeIN, the basal cell atypia is more pronounced, and there is the presence of cells with prominent eosinophilic cytoplasm (C). HPV-independent PeIN may also comprise verrucous/verruciform precursor lesions (D) with hypergranulosis and parakeratosis.

votes and 60% votes, respectively). We surmise that in the coming years, the evidence in favor of this dichotomous split in classifying HPV-independent PeIN based on p53 mutation may gain importance. Similarly, the utility of Ki67 remains questionable in routine,¹⁴ and a majority of participants (72%) do not use it to distinguish squamous hyperplasia and differentiated PeIN.

There was agreement on routinely reporting PeIN and lichen sclerosis associated with invasive penile cancer. However, the site and subtyping of lichen sclerosis (lichenoid, band-like, lymphocytic depleted, and mixed) did not align as a consensus among the participants.^{24,31} The concept of not reporting PeIN in close apposition with an invasive focus similar to the shoulder area of a urothelial carcinoma did not find credibility among the respondents, and most agreed that PeIN should be reported irrespective of their proximity to an invasive carcinoma (69%

consensus). Also, margin involvement by PeIN, as expected, was a favored reporting parameter by 99% of voters, which is a standard guideline in all datasets and a risk factor for local recurrence. The summary of these consensus statements is presented in Table 3.

In conclusion, this consensus paper highlights evolving practices in reporting penile precursor lesions and brings forth a strong emphasis on HPV association and the utility of immunohistochemistry. However, variation exists in subtyping, issues of grading, and molecular testing for HPV detection. Consensus is well-formed around updated terminologies (PeIN), routine use of p16 IHC for HPV association, and the inclusion of margin involvement by PeIN, as well as the presence of lichen sclerosis in reports. However, areas like subclassification of HPV-independent lesions and PeIN grading require further study and evidence-based standardization.

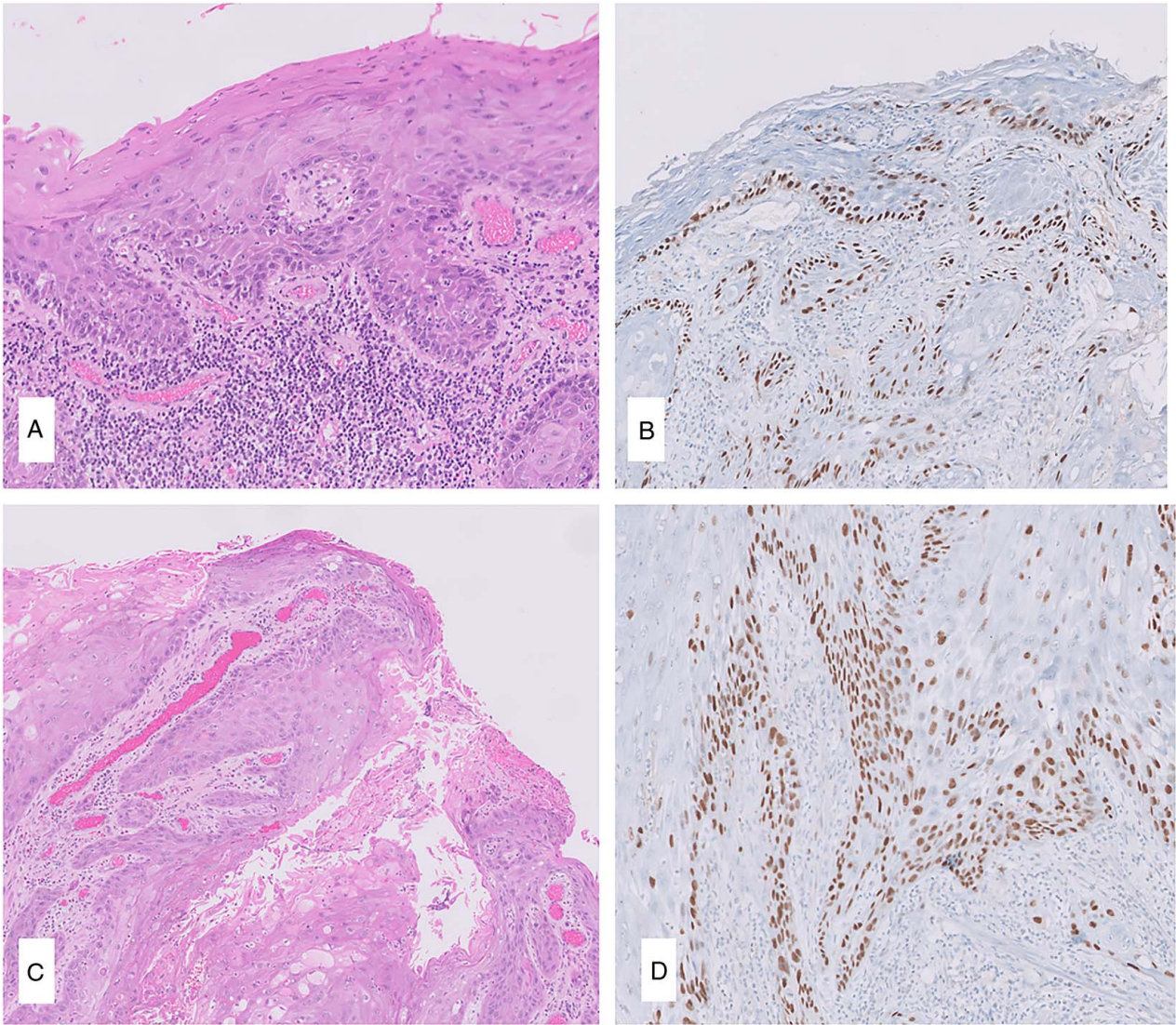


FIGURE 7. HPV Independent PeIN-subtle abnormalities in the basal layer (A), which is highlighted by a basal p53 mutant pattern (B). Also, note the lichenoid inflammation in this (A). A papillary pattern of HPV-independent PeIN (C) showing mutant p53 expression in the basal/parabasal location (D).

TABLE 3. Summary of the penile cancer precursors consensus meeting

PeIN is classified into 2 categories: HPV-associated and HPV-independent
p16 immunohistochemistry (IHC) is the preferred method to distinguish between these 2 types
HPV-associated PeIN can be further sub-classified morphologically as basaloid, warty, mixed, or NOS (not otherwise specified)
Additional studies are needed to evaluate the role of p53 immunohistochemistry for routine daily surgical pathology in HPV-independent PeIN.
Diagnosis of HPV-independent PeIN continues to rely on histologic and immunohistochemical features (p16 negative). They can be further sub-classified morphologically as differentiated (p53 overexpression) and verrucous (p53 wild-type) precursors

ACKNOWLEDGMENTS

The authors thank all the respondents to the ISUP membership survey and acknowledge Franklin AI for venue sponsorship.

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(Germany), James Brugarolas (USA), Matteo Brunelli (Italy), Lukas Bubendorf (Switzerland), Katie Buzacott (Australia), Birgitte Carlsen (Norway), Alcides Chaux (Paraguay), Fei Chen (USA), Liang Cheng (USA), Arul Chinnaiyan (USA), Roselyne Choiniere (Netherlands), Alessia Cimadamore (Italy), 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), Angelo DeMarzo (USA), 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 Fichthner (Germany), Samson Fine (USA), Achim Fleischmann (Switzerland), Jacqueline Fontugne (France), Rongbin Ge (USA), Gianluca Giannarini (Italy), Giovanna Giannico (USA), Timothy Gilligan (USA), Jennifer Gordetsky (USA), Nancy Greenland (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), Jiaoti Huang (USA), Kenneth Iczkowski (USA), Rafael Jimenez (USA), Merce Jorda (USA), Ashish Kamat (USA), Payal Kapur (USA), Seema Kaushal (India), James Kench (Australia), Margaret Knowles (United Kingdom), Glen Kristiansen (Germany), Li Lei (USA), Subodh Lele (USA), João Lobo (Portugal), Massimo Loda (USA), Leendert Looijenga (Netherlands), Antonio Lopez-Beltran (Spain), Tamara Lotan (USA), Anand Loya (Denmark), Fiona Maclean (Australia), Alopa Malaviya (United Kingdom), Guido Martignoni (Italy), Rohit Mehra (USA), Santosh Menon (India), Laura Mertens (Netherlands), Holger Moch (Switzerland), Sambit Mohanty (India), Rodolfo Montironi (Italy), Helmut Mühleisen (Germany), Andrea Necchi (Italy), George Netto (USA), Ngoc-Nhu Jennifer Nguyen (USA), Maya Nourieh (France), Mikko Nyman (Finland), Pedro Oliveira (United Kingdom), Declan O'Rourke (United Kingdom), Adeboye Osunkoya (USA), Gladell Paner (USA), Ewa Rajpert-De Meyts (Denmark), Maria Raspollini (Italy), Timothy Ratliff (USA), Sigrid Regauer (Austria), Henning Reis (Germany), Ohashi Riuko (Switzerland), Antonio Rodriguez-Calero (Switzerland), Jeffrey Ross (USA), Diego Sanchez (Paraguay), Ankur Sangoi (USA), Fanni Santa (USA), Steven Shen (USA), Brian Shuch (USA), Steven Smith (Croatia), Philippe Spiess (USA), John Strigley (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), Geert JLH van Leenders (Netherlands), Bas van Rhijn (Netherlands), Funda Vakar Lopez (USA), Murali Varma (United Kingdom), 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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