International Society of Urological Pathology (ISUP) Multidisciplinary Consensus Conference on Premalignant and Precursor Lesions of the Genitourinary Organs

Current Evidence and Future Directions

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Cancer precursor lesions stand at the nexus of surgical pathology, linking morphology with tumor biology, carcinogenesis, cancer screening, risk stratification, and clinical decision-making.[1] In the genitourinary organs, however, precursor lesions present distinct complexities: some are well defined with established clinical management strategies, whereas others remain controversial, poorly reproducible, and of uncertain clinical significance. Rapid advances in molecular diagnostics, imaging modalities, and early-detection strategies have further disrupted established frameworks, necessitating renewed evaluation of nomenclature, diagnostic criteria, and reporting standards. Taken together, these developments have shifted the focus of precursor lesions from a historically conceptual topic toward entities with direct diagnostic, prognostic, and therapeutic implications.

Against this backdrop, the International Society of Urological Pathology (ISUP) convened a Multidisciplinary Consensus Conference on Cancer Precursor Lesions of the Genitourinary Organs on September 12, 2024, in Florence, Italy. The objectives of the meeting were to define established and putative precursor lesions across genitourinary organs, refine classification schemes and terminology; provide practical recommendations for pathology reporting; clarify the role of ancillary studies, including immunohistochemistry and molecular testing; and synthesize the literature to inform evolving clinical management guidelines. Five organ-specific working groups - prostate, urinary bladder, kidney, testis, and penis -conducted structured literature reviews, as well as pre-meeting and in-meeting voting and discussion. The resulting manuscripts were published in *The American Journal of Surgical Pathology* and reflect both areas of strong consensus and domains where evidence remains incomplete, underscoring the uneven landscape of precursor biology across genitourinary organs.

WORKING GROUP 1: PRECURSOR LESIONS OF THE PROSTATE

Among all genitourinary organs, the prostate illustrates most clearly how advances in imaging, sampling strategies, and molecular pathology have reshaped the clinical relevance of traditional precursor lesions. Precursor lesions of prostatic adenocarcinoma have been investigated for decades, yet their clinical relevance has

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shifted substantially in the era of precision cancer screening, multiparametric MRI-integrated biopsy strategies, and emerging molecular subclassification. Working Group 1 focused on high-grade prostatic intraepithelial neoplasia (HGPIN), intraductal carcinoma of the prostate (IDC-P), atypical intraductal proliferation (AIP), atypical adenomatous hyperplasia (AAH/adenosis), and proliferative inflammatory atrophy (PIA).[2]

HGPIN remains the best-characterized epithelial precursor lesion from a biologic standpoint, sharing numerous molecular alterations with invasive carcinoma, including telomere shortening, GSTP1 promoter hypermethylation, MYC amplification, and occasional ERG rearrangements.[3] However, the group emphasized that the clinical utility of isolated HGPIN has markedly diminished. Contemporary series demonstrate cancer detection rates after isolated HGPIN comparable to those following benign biopsies, largely reflecting improved sampling and imaging protocols.

The Working Group reached consensus that low-grade PIN should not be reported and that HGPIN need not be reported in specimens containing invasive carcinoma or atypical small acinar proliferation suspicious but not diagnostic of malignancy (ASAP). Importantly, although unifocal HGPIN carries uncertain significance, multifocal isolated HGPIN retains modest predictive value and should continue to be reported in biopsy specimens (Table 1).

In contrast, IDC-P emerged as a lesion of major contemporary importance. IDC-P is strongly associated with high-grade, high-stage disease, adverse molecular alterations (PTEN loss, TP53 mutations), and poor clinical outcomes. Its identification on biopsy has direct implications for management, often precluding active surveillance. The Working Group reaffirmed that dense cribriform or solid intraductal architecture is sufficient for diagnosis, even in the absence of marked nuclear pleomorphism.

AIP was recognized as an intermediate-risk intraductal lesion, biologically and clinically distinct from both HGPIN and IDC-P. Importantly, the consensus recommended that cribriform HGPIN be redesignated as AIP. AIP on biopsy-whether isolated or associated with grade group 1 carcinoma-should be reported with an explanatory comment, given its substantial association with unsampled high-grade tumor and less favorable prognosis.[2]

AAH/adenosis and PIA were acknowledged as lesions of limited clinical impact. Although both may share selected molecular features with prostatic adenocarcinoma, evidence supporting their role as actionable precursors remains insufficient. Routine reporting was therefore not required, although reporting of these lesions may be appropriate in the context of differential diagnosis wtih cancer mimickers.

WORKING GROUP 2: PRECURSOR LESIONS OF THE URINARY BLADDER

Precursor lesions of the urinary bladder exemplify the ongoing dissonance between established morphologic concepts and evolving classification systems. Working Group 2 addressed flat, papillary, squamous, and glandular precursor lesions of the urinary bladder, with particular attention to inconsistent terminology across WHO classifications and variable diagnostic reproducibility.[4]

A major outcome of the consensus was reaffirmation of urothelial dysplasia as a distinct and valid diagnostic entity. Most participants supported continued use of this term when cytologic and architectural atypia exceed reactive changes but fall short of carcinoma in situ (CIS). CIS itself remains the archetypal flat precursor lesion, with clear clinical relevance and therapeutic consequences.[5] The Working Group emphasized that diagnosis should remain morphology-driven, with CK20 and p53 immunohistochemistry serving as supportive ancillary tests in difficult cases.

For papillary lesions, the Working Group strongly favored papillary urothelial hyperplasia as the preferred terminology for early papillary proliferations lacking true fibrovascular cores or cytologic atypia (Table 1). Accumulating molecular data-demonstrating shared alterations such as TERT promoter mutations and chromosome 9 loss-support papillary urothelial hyperplasia as a precursor in the tumorigenesis of papillary pathway, rather than a purely reactive process.[6] In contrast, urothelial papilloma was a benign lesion, not regarded as a precursor lesion.

Squamous precursor lesions generated strong consensus. Keratinizing squamous metaplasia was recognized as preneoplastic, particularly in appropriate clinical contexts, and squamous dysplasia should be reported and graded when present. In contrast, non-keratinizing squamous metaplasia, especially in the trigone of women, was reaffirmed as benign.

Glandular precursor lesions remain an area of uncertainty. Although cystitis glandularis and intestinal metaplasia are generally considered benign reactive processes, intestinal metaplasia with dysplasia was recognized as potentially preneoplastic and warrants explicit reporting.

WORKING GROUP 3: PRECURSOR LESIONS OF THE KIDNEY

Among genitourinary organs, the kidney presents perhaps the greatest conceptual challenges in defining precursor lesions. The Working Group emphasized that, unlike many other epithelial malignancies in other organ sites, renal cell carcinomas often lack co-existing morphologically distinct precursor lesions.[7]

Papillary adenoma remains the only well-established renal precursor lesion (Table 1). The consensus reaffirmed existing WHO criteria, including size and cytologic thresholds, and emphasized its biologic continuity with papillary renal cell carcinoma, supported by shared chromosomal gains of chromosomes 7 and 17.[8]

In contrast, no morphologic precursor has been identified for sporadic clear-cell renal cell carcinoma. Although von Hippel–Lindau (VHL) disease provides a

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TABLE 1. Key Findings of the International Society of Urological Pathology (ISUP) Multidisciplinary Consensus Conference on Premalignant and Precursor Lesions of the Genitourinary Organs 1.

Prostate • Low-grade PIN should not be reported.
• High-grade PIN should be reported selectively, primarily when multifocal and/or isolated on biopsy.
• High-grade PIN (HGPIN) should not be reported when adjacent to invasive carcinoma or ASAP.
• Intraductal carcinoma of the prostate (IDC-P) is a marker of aggressive disease and may be diagnosed based on dense cribriform or solid architecture even without marked nuclear pleomorphism.
• Cribriform HGPIN should be redesignated as atypical intraductal proliferation (AIP).
• AIP on biopsy warrants reporting with an explanatory comment, particularly when isolated or associated with grade group 1 carcinoma.
• Routine reporting of PIA and AAH/adenosis is not required.
Urinary Bladder
• Carcinoma in situ (CIS) remains the prototypical flat precursor lesion with direct clinical implications.
• Urothelial dysplasia is a valid diagnostic entity and should be recognized when atypia exceeds reactive changes, but falls short of carcinoma in situ.
• Papillary urothelial hyperplasia is the preferred term for early papillary proliferations and may represent a true precursor.
• Keratinizing squamous metaplasia and squamous dysplasia are putative precursor lesions and should be reported.
• Intestinal metaplasia with dysplasia may represent a precursor and should be reported
• Ancillary studies (eg, CK20, p53) should be used judiciously in selected cases.
Kidney
• Papillary adenoma is the only well-established renal precursor lesion.
• In von Hippel–Lindau disease, small clear cell nodules and cysts represent early neoplastic lesions.
• No established precursor exists for sporadic clear-cell renal cell carcinoma.
• Use descriptive terminology for cystic lesions (eg, "cyst with epithelial proliferation", "renal papillary hyperplasia").
• Terms such as "tumorlet," "microtumor," or "incipient tumor" are acceptable in hereditary conditions.
• Insufficient evidence to designate renal tubular dysplasia as a renal cancer precursor.
Testis
• Germ cell neoplasia in situ (GCNIS) is the preferred term and should be reported when present.
• Use standardized terminology for seminoma with intratubular non-seminomatous germ cell neoplasia.
• OCT3/4 is the preferred primary immunohistochemical marker.
• Gonadoblastoma is a precursor lesion, arising in the setting of disorders of sex development.
Penis
• Penile intraepithelial neoplasia (PeIN) is the preferred diagnostic term and categorized as HPV-associated or HPV-independent
• HPV-associated PeIN may be further subtyped as basaloid, warty, mixed, or NOS.
• Further subtyping of HPV-independent PeIN is not required.
• Do not grade PeIN, all PeINs are considered high grade
• p16 immunohistochemistry is recommended to assess HPV status.
• Routine use of p53 immunohistochemistry or HPV genotyping is not recommended.
• Report margin status and association with lichen sclerosus when present.

compelling model, characterized by numerous microscopic clear-cell proliferations, no analogous lesion has been convincingly demonstrated in sporadic tumors.[9] This absence of a defined sporadic precursor underscores the biologic distinctiveness of renal tumorigenesis and cautions against forced analogies to other organ systems.[10] In hereditary settings, the Working Group endorsed pragmatic terminology, allowing the use of descriptors such as "tumorlet," "microtumor," or "incipient tumor" to acknowledge the morphologic and biological continuum of these lesions.[7]

Cyst-associated epithelial proliferations were also addressed in kidney precursor working group. In acquired cystic kidney disease (ACKD), epithelial tufting and stratification may represent early neoplastic change; the preferred term is "cyst with epithelial proliferation", reserving tumor diagnoses for lesions with solid growth. In autosomal dominant polycystic kidney disease (ADPKD), renal papillary hyperplasia was recommended as a descriptive term, acknowledging uncertainty regarding true precursor potential.

Evidence for renal tubular dysplasia as a bona fide precursor lesion is currently insufficient, and routine use of the term is not recommended. Similarly, the entity referred to as "atypical renal cyst" remains elusive due to lack of clear diagnostic criteria and clinical data.

WORKING GROUP 4: PRECURSOR LESIONS OF THE TESTIS

Testicular germ cell tumors offer one of the most coherent models of precursor-to-invasive progression in tumorigenesis.[11] For testicular neoplasia, the focus of the Working Group was less on redefining precursor biology and more on harmonizing diagnostic practice. Working Group 4 focused primarily on germ cell neoplasia in situ (GCNIS) and real-world diagnostic practice patterns.[12]

There was near-universal consensus that GCNIS is the definitive precursor lesion for postpubertal (type II) germ cell tumors and that this term should be used exclusively (Table 1). GCNIS should be reported when identified, particularly in association with invasive germ cell tumors, to confirm the pathogenetic pathway.

OCT3/4 should be used as the preferred immunohistochemical marker, with broad panels generally unnecessary.[13] Notably, no consensus was reached on whether immunohistochemistry is mandatory in all cases.

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Molecular testing for isochromosome 12p was not required for routine diagnosis.

Another area of strong consensus involved terminology for seminoma associated with intratubular nonseminomatous elements. "Seminoma with intratubular non-seminoma" was the preferred designation. This terminology allows accurate description of intratubular embryonal carcinoma, yolk sac tumor, trophoblastic cells, or teratoma without incorrectly classifying the tumor as a mixed invasive germ cell tumor, which would have significant therapeutic implications. The work highlights the importance of clear communication with clinicians, ensuring that intratubular findings are not misconstrued as invasive disease components

Gonadoblastoma remains an uncommon but diagnostically complex precursor lesion, typically arising in the setting of disorders of sex development.[14] The survey demonstrated marked variability in immunohistochemical approaches, with respondents using combinations of germ cell markers (OCT3/4, PLAP, CD117) and sex-cord markers (inhibin-A, SOX9, FOXL2). The absence of consensus reflects both the rarity of gonadoblastoma and its intrinsic histologic heterogeneity. This area was explicitly identified as one requiring further standardization and future consensus efforts.

WORKING GROUP 5: PRECURSOR LESIONS OF THE PENIS

Working Group 5 addressed terminology, grading, ancillary testing, and reporting practices for penile precursor lesions, specifically penile intraepithelial neoplasia (PeIN).[15] A major consensus outcome was the unequivocal endorsement of classifying PeIN as HPV-associated versus HPV-independent lesions. This dichotomous framework reflects the distinct morphologic, molecular, and clinical pathways of penile carcinogenesis.

Morphologic subtyping (basaloid, warty, and warty-basaloid) was supported for HPV-associated PeIN, whereas subtyping of HPV-independent lesions remains uncertain (Table 1).

One of the most practice-changing recommendations was the strong consensus against grading PeIN. Grading was deemed poorly reproducible and lacking validated clinical correlation; PeIN should instead be regarded as intrinsically high-grade.

Among ancillary studies, p16 immunohistochemistry was strongly endorsed as a routine ancillary test for determining HPV status. In contrast, routine p53 immunohistochemistry and HPV molecular genotyping were not recommended and should be reserved for select discordant cases.

Reporting of margin involvement by PeIN and documentation of associated lichen sclerosus were strongly supported due to their clinical relevance.

CONCLUSIONS

Collectively, these consensus documents highlight that precursor lesions of the genitourinary tract cannot be approached as a uniform category. Their biological underpinnings, diagnostic reproducibility, and clinical consequences vary substantially by organ and disease context.[16] Notably, organs with well-defined morphologic precursors, such as prostate and testis, contrast sharply with those in which precursor concepts remain limited or indirect, such as kidney, underscoring the need for organ-specific diagnostic frameworks.

By defining what is established, what is actionable, and what remains uncertain, this series provides a contemporary framework for diagnostic practice while identifying priorities for future investigation. The ISUP Multidisciplinary Consensus Conference on Cancer Precursor Lesions represents a major collaborative effort to standardize diagnostic terminology and reporting practices, and to advance the biologic understanding of premalignant and precursor lesions across the genitourinary organs. These consensus guidelines will serve as essential references for pathologists, urologists, and oncologists, and provide a foundation for future research, nosologic refinement, and clinical guideline development.

REFERENCES

1. Faupel-Badger J, Kohaar I, Bahl M, et al. Defining precancer: a grand challenge for the cancer community. *Nat Rev Cancer*. 2024; 24:792–809.
2. Iczkowski KA, De Marzo AM, Agarwal N, et al. International Society of Urological Pathology Consensus on Cancer Precursor Lesions. Working Group 1: The Prostate. *Am J Surg Pathol*. 2025; 49:e33–e45.
3. Bostwick DG, Cheng L. Precursors of prostate cancer. *Histopathology*. 2012;60:4–27.
4. Downes MR, Lopez-Beltran A, Contieri R, et al. International Society of Urological Pathology Consensus Meeting 2024: Working Group 2 Preneoplastic and Precursor Lesions of the Urinary Bladder. *Am J Surg Pathol*. 2025;49:e46–e57.
5. Casey RG, Catto JW, Cheng L, et al. Diagnosis and management of urothelial carcinoma in situ of the lower urinary tract: a systematic review. *Eur Urol*. 2015;67:876–888.
6. Cheng L, Lopez-Beltran A, Wang M, et al. Frequent telomerase reverse transcriptase promoter and fibroblast growth factor receptor 3 mutations support the precursor nature of papillary urothelial hyperplasia of the urinary bladder. *Mod Pathol*. 2023; 36:100151.
7. Williamson SR, Wobker S, Mehra R, et al. International Society of Urological Pathology Consensus on Cancer Precursor Lesions: Working Group 3 Preneoplastic and Precursor Lesions of the Kidney. *Am J Surg Pathol*. 2026. (in press).
8. Brunelli M, Eble JN, Zhang S, et al. Gains of chromosomes 7, 17, 12, 16 and 20, and loss of Y occur early in the evolution of papillary renal cell neoplasia: a fluorescent in situ hybridization study. *Mod Pathol*. 2003;16:1053–1059.
9. Kaelin WG. Von Hippel-Lindau disease: insights into oxygen sensing, protein degradation, and cancer. *J Clin Invest*. 2022;132: e162480.
10. Frew IJ, Moch H. A clearer view of the molecular complexity of clear cell renal cell carcinoma. *Annu Rev Pathol Mech Dis*. 2015;10: 263–89.
11. Cheng L, Albers P, Berney DM, et al. Testicular cancer. *Nat Rev Dis Primers*. 2018;4:29.
12. Bremmer F, Colecchia M, Collins K, et al. International Society of Urological Pathology Consensus on Cancer Precursor Lesions: Working Group 4 Precursor Lesions of the Testis. *Am J Surg Pathol*. 2026. (in press).
13. Jones TD, Ulbright TM, Eble JN, et al. OCT4: a sensitive and

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specific biomarker for intratubular germ cell neoplasia of the testis. *Clin Cancer Res*. 2004;10:8544–8547.
14. Roth LM, Cheng L. Gonadoblastoma: origin and outcome. *Hum Pathol*. 2020;100:47–53.
15. Menon S, Sanchez D, Chaux A, et al. 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. *Am J Surg Pathol*. 2026. (in press).
16. Cheng L, MacLennan GT, Bostwick DG. *Urologic Surgical Pathology*, Fifth edition. Elsevier, Philadelphia, PA. 2026.

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