COLLEGE of AMERICAN PATHOLOGISTS

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The Lower Anogenital Squamous Terminology Standardization Project for HPV-associated Lesions: Background and Consensus Recommendations

From the College of American Pathologists and American Society for Colposcopy and Cervical Pathology

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RECOMMENDATIONS

Squamous Intraepithelial Lesions

1. A unified histopathological nomenclature with a single set of diagnostic terms is recommended for all HPV-associated preinvasive squamous lesions of the lower anogenital tract.
2. A 2-tiered nomenclature is recommended for non-invasive HPV-associated squamous proliferations of the lower anogenital tract which may be further qualified with the appropriate –IN terminology.
   -IN refers to the generic intraepithelial neoplasia terminology, without specifying the location. For a specific location the appropriate complete term should be used. Thus for an –IN3 lesion: cervix = CIN3, vagina = VaIN3, vulva = VIN3, anus = AIN3, perianus = PAIN3, and penis = PeIN3
3. The recommended terminology for HPV-associated squamous lesions of the lower anogenital tract is Low Grade Squamous Intraepithelial Lesion (LSIL) and High Grade Squamous Intraepithelial Lesion (HSIL), which may be further classified by the applicable –IN subcategorization.

Superficially Invasive Squamous Cell Carcinomas (SISCCA)

1. The term *"superficially invasive squamous cell carcinoma (SISCCA)"* is recommended for minimally invasive squamous cell carcinoma of the lower anogenital tract that has been completely excised and is potentially amenable to conservative surgical therapy.
   Note: Lymphovascular invasion (LVI) and pattern of invasion are not part of the definition of SISCCA, with the exception of penile carcinoma.
2. For cases of invasive squamous carcinoma with positive biopsy/resection margins, the pathology report should state whether:
   The examined invasive tumor exceeds the dimensions for a SISCCA (defined below)
   a. *OR*
      The examined invasive tumor component is less than or equal to the dimensions for a SISCCA and conclude that the tumor is *"At least a superficially invasive squamous carcinoma."*
3. In cases of SISCCA, the following parameters should be included in the pathology report:
   The presence or absence of lymphovascular invasion (LVI).
   The presence, number, and size of independent multifocal carcinomas (after excluding the possibility of a single carcinoma).
4. CERVIX: SISCCA of the cervix is defined as an invasive squamous carcinoma that:
   Is not a grossly visible lesion, AND
   Has an invasive depth of ≤ 3 mm from the basement membrane of the point of origin, AND
   Has a horizontal spread of ≤ 7 mm in maximal extent, AND
   Has been completely excised.
5. VAGINA: No recommendation is offered for early invasive squamous carcinoma of the vagina.
   Due to the rarity of primary SCC of the vagina, there are insufficient data to define early invasive squamous carcinoma in the vagina.
6. ANAL CANAL: The suggested definition of superficially invasive squamous cell carcinoma (SISCCA) of the anal canal is an invasive squamous carcinoma that:
   Has an invasive depth of ≤ 3 mm from the basement membrane of the point of origin, AND
   Has a horizontal spread of ≤ 7 mm in maximal extent, AND
   Has been completely excised.
7. VULVA: Vulvar SISCCA is defined as an AJCC T1a (FIGO 1A) vulvar cancer.
   No change in the current definition of T1a vulvar cancer is recommended.
   Current AJCC definition of T1a vulvar carcinoma:
   Tumor 2 cm or less size, confined to the vulva or perineum AND
   Stromal invasion of 1 mm or less.
   Note: The depth of invasion is defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.

8. PENIS: Penile SISCCA is defined as an AJCC T1a.
   No change in the current definition of T1a penile cancer is recommended.
   Current AJCC definition of T1a penile carcinoma:
   Tumor that invades only the subepithelial connective tissue, AND
   No lymphovascular invasion AND
   Is not poorly differentiated (i.e., grade 3-4).
9. SCROTUM: No recommendation is offered for early invasive squamous carcinoma of the scrotum.
   Due to the rarity of primary SCC of the scrotum, there is insufficient evidence to make a recommendation regarding the current AJCC staging of early scrotal cancers.
10. PERIANUS: The suggested definition for SISCCA of the perianus is an invasive squamous carcinoma that:
    Has an invasive depth of ≤ 3 mm from the basement membrane of the point of origin, AND
    Has a horizontal spread of ≤ 7 mm in maximal extent, AND
    Has been completely excised.

Biomarkers in HPV-associated Lower Anogenital Squamous Lesions

1. p16 IHC is recommended when the H&E morphologic differential diagnosis is between precancer (─IN 2 or ─ IN 3) and a mimic of precancer (e.g. processes known to be not related to neoplastic risk such as immature squamous metaplasia, atrophy, reparative epithelial changes, tangential cutting, etc.).
   Strong and diffuse block positive p16 results support a categorization of precancerous disease.
2. If the pathologist is entertaining an H&E morphologic interpretation of ─IN 2 [under the old terminology; which is a biologically equivocal lesion falling between the morphologic changes of HPV infection (low grade lesion) and precancer], p16 IHC is recommended to help clarify the situation. Strong and diffuse block positive p16 results support a categorization of precancer. Negative or non-block positive staining strongly favors an interpretation of low grade disease or a non-HPV associated pathology.
3. p16 is recommended for use as an adjudication tool for cases in which there is a professional disagreement in histologic specimen interpretation, with the caveat that the differential diagnosis includes a precancerous lesion (─IN2 or ─IN3).
4. WG4 recommends against the use of p16 IHC as a routine adjunct to histologic assessment of biopsy specimens with morphologic interpretations of negative, –IN1, and –IN3.
   a. SPECIAL CIRCUMSTANCE
   p16 IHC is recommended as an adjunct to morphologic assessment for biopsy specimens interpreted as ≤ ─IN1 that are at high risk for missed high-grade disease, which is defined as a prior cytologic interpretation of HSIL, ASC-H, ASC-US/HPV16 +, or AGC (NOS).
   Any identified p16 positive area must meet H&E morphologic criteria for a high grade lesion to be reinterpreted as such.

A. Panel Composition

The College of American Pathologists (CAP) Pathology and Laboratory Quality Center (the CAP Center) and the American Society for Colposcopy and Cervical Pathology (ASCCP) convened a Steering Committee (SC) and five Work Groups (WG) consisting of surgical pathologists, gynecologic pathologists, dermatopathologists, and medical and surgical specialists including gynecologists, gynecologic oncologists, dermatologists, infectious disease specialists and surgeons. Members and advisors included representatives from both organizations and other clinical specialties. Both organizations utilized their respective organization's approval processes in formal review and appointment of the project, chairs and work group members.

The following 5 Work Groups (WG) were formed to review the evidence and draft consensus recommendations:

- WG1: Historical Review of Lower Anogenital Tract HPV-associated Squamous Lesion Terminology
- WG2: Squamous Intraepithelial Lesions
- WG3: Superficially Invasive Squamous Cell Carcinomas (SISCCA)
- WG4: Biomarkers in HPV-associated Lower Anogenital Squamous Lesions
- WG5: Implications and Implementation of Standardized Terminology

B. Management of Conflict of Interest (COI)

All Steering Committee, work group members and advisors complied with the CAP conflicts of interest policy (in effect October 2010) which required disclosure of financial or other interests that may have an actual, potential or apparent conflict. The CAP Center and ASCCP used the following criteria:

Nominees who have the following conflicts may be excused from the panel:

a. Stock or equity interest in a commercial entity that would likely be affected by the guideline or consensus statement
b. Royalties or licensing fees from products that would likely be affected by the guideline or consensus statement
c. Employee of a commercial entity that would likely be affected by the guideline or consensus statement

Nominees who have the following potentially manageable direct conflicts may be appointed to the panel:

a. Patents for products covered by the guideline or consensus statement
b. Member of an advisory board of a commercial entity that would be affected by the guideline or consensus statement
c. Payments to cover costs of clinical trials, including travel expenses associated directly with the trial
d. Reimbursement from commercial entity for travel to scientific or educational meetings

Steering Committee, members and advisors were required to disclose new conflicts at each conference call and submit an updated COI form prior to the consensus conference. The COI information (2011 and 2012) was made available to participants during the conference.

ASCCP and CAP covered the cost of developing this project; no industry funds were used in the development of the consensus statement.

C. Evidence

1. Information Source, Search and Study Selection

The scope, key questions, search terms and literature review results are identified in Appendix A. WG1 conducted its literature review outside the review framework as the WG did not make specific recommendations; WG5 did not complete a literature review.

A computerized search was conducted during the period March 2011 through January 2012 for Work Groups 1 through 4 with the following electronic databases: OVID MEDLINE, PubMed, Wiley Cochrane Library, and OCLC WorldCat, for English language articles only. All study designs and publication types were included. Reference lists from identified articles were scrutinized for articles not identified in the searches.

Screening and data extraction were completed using DistillerSR (Evidence Partners, Ottawa, Canada) for WG2, WG3 and WG4. Each identified article underwent an inclusion-exclusion process, dual-independent reviews conducted by co-chairs and WG members. Based on each WG's inclusion/exclusion criteria (Table 1) articles were kept for data extraction, as "indirect background material" or excluded from further

review. Articles with two differing votes were considered in conflict. Conflicts included the “uncertain” reviews at the title/abstract level and the “indirect background material” reviews at the full text level. These articles were available for discussion or background references. Conflicts were adjudicated by both reviewers for WG2 and WG3 and by co-chair referees when conflicts could not be resolved. Co-chairs alone adjudicated WG4 conflicts.

For WG2 (Squamous Intraepithelial Lesions) 1,909 studies met the search term requirements and 186 studies were included for data extraction. For WG3 (Superficially Invasive Squamous Cell Carcinomas) 1,863 studies met the search term requirements and 194 studies were included for data extraction. For WG4 (Biomarkers in HPV-associated Lower Anogenital Squamous Lesions) 2,291 studies met the search term requirements, 72 studies were included for data extraction, and 18 studies identified for grading.

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Table 1 Title/Abstract and Full Text Inclusion-Exclusion Criteria

Work Group	Inclusion Criteria	Exclusion Criteria
WG2 Squamous Intraepithelial Lesions	Articles directly related to scope and key questions for histopathologic tiering terminology	Non-human or incorrect body site; Non HPV-related dermatologic or pathologic process; Fully invasive or related to head/neck cancers; Adenocarcinoma related to body site(s); Cytology related; Major molecular focus; Radiology/radiation or any other clinical therapy not directly related; Reproductive intent
WG3 Superficially Invasive Squamous Cell Carcinomas	Articles directly related to scope and key questions for histopathologic terminology of early invasive, minimally invasive, microinvasive and superficially invasive cancers	Non-human or incorrect body site; Non HPV-related dermatologic or pathologic process; Fully invasive or related to head/neck cancers; Adenocarcinoma related tobody site(s); Cytology related; Major molecular focus; Radiology/radiation or any other clinical therapy not directly related; Reproductive intent
WG4 Biomarkers in HPV-associated Lower Anogenital Squamous Lesions	Clinical validation studies (e.g., established sensitivity/specificity, performance against histological standard); Size of study $\geq$ 100 cases/subjects; Cytology studies using histologic standards/true (3-way) adjudication may be included	Non-human or incorrect body site; Basic science or pure molecular study; Preliminary hypothetical testing – analytical or non clinical validation study; Statistically underpowered or no critical direct bearing; Does not have histologic gold-standard and/or histology is non-adjudicated; Non HPV-associated neoplasia related study; Reproductive intent; Study giving only clinical or management information (no pathologic endpoint)

2. **Quality of Evidence:**

A quality of evidence review for WG4 (Biomarkers in HPV-associated Lower Anogenital Squamous Lesions) was conducted as the recommendations were driven most by the data extractions and an assessment of the quality of the data in this WG was most important. WG2 and WG3 completed and reviewed the results of their respective data extraction and proposed recommendations based upon expert opinion with appropriate references provided.

WG4: Biomarkers in HPV-associated Lower Anogenital Squamous Lesions

The initial recommendations, and the evidence used to support them, were reviewed by an independent reviewer with experience in the development of evidence-based guidelines (Evan R. Myers, M.D., M.P.H., Duke University Department of Obstetrics & Gynecology); articles excluded during the initial search and review phase were not re-reviewed. Based on the reviewer's overall assessment of the quality of the evidence for test characteristics and observer variability, WG4's recommendations were framed using "recommend" if the recommendations are unlikely to change

based on further evidence, and “suggest” if the recommendations are most likely correct but could be better supported by additional data.

Review of the eighteen papers cited for the recommendations found 2 papers directly comparing the performance of hematoxylin and eosin (H&E) alone vs H&E + p16 for cervical disease using consensus histology as a reference standard, and 4 reporting test characteristics for H&E + p16 alone(1-6) (Table 2). For each of these papers, sensitivity, specificity, and 95% confidence intervals were directly calculated from the data provided. In addition, 5 papers provided data on interobserver variability, as measured by kappa statistics, for H&E alone vs H&E + p16(1-3, 7, 8) (Table 3).

The quality of the evidence for the test characteristics of H&E p16 is moderate to high. Both of the direct comparisons showed statistically significant increases in sensitivity for a consensus histologic diagnosis of CIN2+, and increases in sensitivity for CIN3+ (significant in the Galgano paper, not quite significant in the Bergeron paper)(2, 3). Specificity was decreased with the addition of p16, although the absolute decrease was much larger in the Galgano paper than in the Bergeron study(2, 3). In the papers without a comparator, sensitivities were all 95% or higher at both thresholds.

The quality of the evidence for improved consistency of readings with p16 is high. All 5 studies measuring observer variability found significant or close to significant improvement in consistency of readings with the addition of p16 to H&E. The clinical significance of this is supported by the data presented in Galgano et al of the sensitivity and specificity for individual pathologists(3).

Factors contributing to the high quality of evidence included (1) consistency of results across multiple studies and settings, (2) precision of results, and (3) low risk of bias in the study designs. Factors decreasing the quality of evidence included (1) relative indirectness in terms of specific clinical outcomes—in particular, the association of CIN2 lesions, even if based on consensus histology, with cancer, and (2) indirectness in terms of setting. The two studies involving direct comparisons were both performed in settings outside of general US practice, either Europe or a single academic institution where institutional bias in terms of histologic thresholds may have lowered sensitivity and raised specificity for histology alone(2, 3).

Based on the quality of the reviewed evidence, there is a high degree of certainty that use of p16 leads to improved sensitivity but decreased specificity compared to H&E alone, with substantially improved consistency between observers. This suggests that use of p16 in accordance with WG4 Recommendations #1-3 would result in improved clinical outcomes, but there is a lack of direct evidence about the impact of implanting these recommendations in a general United States population. This especially raises concern about the potential for overtreatment if recommendations are not followed; this concern specifically led to the development of WG4 Recommendation #4.

The quality of the evidence for superior sensitivity of H&E/p16 is high to moderate. In the clinical setting described in WG4 Recommendation 4a, where there is a higher pretest probability of precancer, the likelihood of a false positive is reduced, and the importance of detecting true disease is increased. Therefore the balance of benefit vs. harm is towards the higher sensitivity but lower specificity of adding p16, and, given the overall quality of the evidence, the use of “recommend” is warranted.

Table 2: Sensitivity and specificity (95% CIs) of p16 vs H&E, (A) or alone, (B) for CIN2+ and CIN3+

STUDY (Author)	p16	Pathology alone	Ref standard	Comment
Table 2 A: Direct comparison to H&E alone(2, 3)				
Galgano	CIN 2+		Consensus histology	Individual pathologist sens for CIN2+ varied from 53.6-100%, spec from 100-82.4%. For CIN 3+, individual pathologist sens varied from 71.4-100%, spec from 96.7-73.9%
	Sens: 86.7% (82.9-90.5%)	Sens: 68.9% (63.8-74.1%)		
	Spec: 82.8% (80.7-85.0%)	Spec: 97.2% (96.2-98.2%)		
	CIN3+			
	Sens: 99.2% (97.8-100%)	Sens: 56.8% (48.4-65.3%)		
	Spec: 74.8% (70.4-77.1%)	Spec: 98.3% (97.6%-99.0%)		
Bergeron	CIN 2+		Consensus histology	
	Sens: 87.6% (86.2-88.4)	Sens: 77.6% (75.9-79.3%)		
	Spec: 87.7% (86.6-88.8%)	Spec: 88.7% (87.7-89.8%)		
	CIN 3+			
	Sens: 80.2% (78.0-82.4%)	Sens: 77.0% (74.6-79.3%)		
	Spec: 89.6% (88.7-90.5%)	Spec: 88.4% (87.5-89.3%)		

Sens = Sensitivity; Spec = Specificity; Ref = Reference; CI = Confidence Interval

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Table 2: Sensitivity and specificity (95% CIs) of p16 vs H&E, (A) or alone, (B) for CIN2+ and CIN3+

STUDY (Author)	p16	Pathology alone	Ref standard	Comment
Table 2 B: p16 alone(1, 4-6)				
Klaes	CIN 2+ Sens: 98.7% (96.9-100.0%) Spec: 81.0% (74.9-87.1%)		Consensus histology	No comparator
	CIN3+ Sens: 98.3% (96.0-100%) Spec: 67.4% (60.7-74.0%)			
Tringler	CIN2+ Sens: 95.3% (90.1-100%) Spec: 88.9% (83.4-94.4%)		Consensus histology	No comparator
	AIS+ Sens: 100% (91.3-100%) Spec: 66.7% (58.6-74.7%)			
Dijkstra	CIN 2+ (all) Sens: 96.7% (94.8-98.6%) Spec: 94.4% (89.0-99.7%)		Consensus histology	No comparator
	CIN 2+ (HPV+ only) Sens: 98.2% (96.7-99.6%) Spec: 89.3% (77.8-100.0%)			
Benevolo	CIN2+ Sens: 96.4% (91.4-100.0%) Spec: 65.9% (56.0-75.8%)		Consensus histology	No comparator
	CIN3+ Sens: 94.4% (87.0-100.0%) Spec: 54.2% (44.8-63.6%)			

Sens = Sensitivity; Spec = Specificity; Ref = Reference; CI = Confidence Interval

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Table 3: Kappas (95% CIs if given in paper) for p16 vs histology alone(1-3, 7, 8)

STUDY (Author)	p16	Histology alone
Galgano	0.87	0.67-0.72
Horn	Punch bx 0.64 Cone bx 0.70	Punch bx 0.49 Cone bx 0.63
Klaes	0.91 (0.84-0.99)	6 categories 0.60 (0.58-0.63) 2 categories 0.71 (0.65-0.78)
Bergeron	All 0.75 (0.73-0.77) Cone bx 0.74 (0.72-0.76) Punch bx 0.75 (0.73-0.77)	All 0.57 (0.54-0.60) Cone bx 0.54 (0.52-0.57) Punch bx 0.58 (0.55-0.61)
Dijkstra	Weighted 0.80 (0.66-0.89) Unweighted 0.76 (0.64-0.84)	Weighted 0.54 (0.38-0.69) Unweighted 0.44 (0.27-0.60)

Bx = Biopsy; CI = Confidence Interval

D. Methods used to produce recommendations

The SC met in January 2011 to refine the scope and form the working groups; the SC and WG co-chairs met in August 2011 and March 2012. All WG members met in March 2012 and additional work was completed through teleconference webinars, collaboration site access (GoDaddy LAST workspace) and electronic mail. The SC and WG co-chairs were responsible for drafting the recommendations for public comment, for conducting the voting session along with the moderators and for writing the final manuscript. Members of WG2, WG3 and WG4 were responsible for completing the full text literature review and data extraction. (Members of WG1 completed the historical review through a literature search and members of WG5 will draft implementations plans.) Once data extraction was completed, the WG co-chairs and members were responsible for reviewing and analyzing the data. Based upon the literature and data reviewed, they drafted the recommendations accordingly. Draft recommendations were posted on the ASCCP website for open comment which was held from January 23 through February 13, 2012. The website received a total of 2,455 visits with 251 comments posted (Table 4).

Table 4: Open Comment Period Results

WG	Number of Visits	Number of Comments
1 - Historical Review of Lower Anogenital Tract HPV-associated Squamous Lesion Terminology	410	27
2 – Squamous Intraepithelial Lesions	684	63
3 - Superficially Invasive Squamous Cell Carcinomas	316	36
4 – Biomarkers in HPV-associated Lower Anogenital Squamous Lesions	708	96
5 - Implications and Implementation of Standardized Terminology	337	29
Total	2,455	251

The WG co-chairs reviewed all comments and shared their documented review to their respective WG members. The draft recommendations were revised as needed prior to the conference based upon the comments received and the WG decisions.

The LAST consensus conference was held March 13 and March 14, 2012, to obtain stakeholder consensus on recommendations proposed by WG2, WG3, and WG4. Thirty five participating organizations (Table 5) sent representatives to review, discuss, and revise as needed before the final vote. Observers in attendance did not vote. Each recommendation required a two-thirds majority (66% or higher) to pass for the final recommendation. Several recommendations not achieving consensus on the first vote were revised by the WGs and submitted for a revote. All recommendations achieved the required majority votes.

The CAP Independent Review Panel (IRP) and the Transformation Program Office Steering Committee (TPOSC) and the ASCCP Board of Directors provided final review and approval of the manuscript.

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Table 5: Participating Organizations at LAST Consensus Conference March 13-14, 2012

Sponsoring Organizations
American Society for Colposcopy and Cervical Pathology College of American Pathologists
Participating Organizations
American Academy of Dermatology American Academy of Family Physicians American Board of Obstetrics and Gynecology American Board of Pathology American Cancer Society American College Health Association American College of Obstetricians & Gynecologists American Sexually Transmitted Diseases Association (ASTDA) American Society for Clinical Pathology American Society for Colon and Rectal Surgeons American Society for Cytopathology The American Society of Dermatopathology American Urological Association Association for Directors of Anatomic and Surgical Pathology Centers for Disease Control and Prevention – Division of Laboratory Science and Standards (Office of Surveillance, Epidemiology and Laboratory Services) Food & Drug Administration International Anal Neoplasia Society International Federation for Cervical Pathology and Colposcopy International Gynecologic Cancer Society International Society for Gynecological Pathologists International Society for the Study of Vulvovaginal Disease National Cancer Institute Nurse Practitioners in Women's Health Papanicolaou Society of Cytopathology Planned Parenthood Federation of America Society of Canadian Colposcopists Society of Gynecologic Oncologists Society of Gynecologic Oncologists of Canada Society of Obstetricians & Gynaecologists of Canada United States and Canadian Academy of Pathology United States Cancer Registries United States Surveillance, Epidemiology and End Results (SEER) Program Veterans Health Administration

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APPENDIX

WG1: Historical Review of Lower Anogenital Tract of HPV-associated Squamous Terminology
Cervix, Vagina, Vulva, Penis, Anus, Perianus and Scrotum

WG1 Scope/Overall Purpose:

- To frame the situation
- To provide the basis for disparate terminologies
- To focus on pathology related issues
- To identify the gap(s) in practice
- To make recommendations for new unified terminology if appropriate

Key Questions (WG1 Charge):

1. What are the different terminologies currently and historically used for HPV-related lower anogenital tract mucocutaneous intraepithelial and primary invasive neoplasia?
2. What are the similarities and differences between these terminologies?
3. Is there a rationale for providing a uniform terminology for the above?
4. How has terminology influenced clinical management?
5. What are the international issues, if any?

WG1 Search Terms: anal, anal canal, anus, Anus Neoplasms, Bowenoid dysplasia, Bowenoid papulosis, Bowen's disease, carcinoma in situ," carcinoma, squamous cell", cervical, Cervical Intraepithelial Neoplasia, cervix, cervix uteri, CIN, Classification, eponyms, Erythroplasia of Queyrat, genital, Historical Article, HPV, Human papillomavirus, ICD-10, intraepithelial neoplasia, nomenclature, nosology, penile, Penile Diseases, Penile Neoplasms, penis, Perianal Intraepithelial Neoplasia, peri-anus, PIN 3, squamous, Taxonomy, Terminology, Terminology as Topic, Uterine Cervical Dysplasia, Uterine Cervical Neoplasms, vagina, Vaginal Neoplasms, VAIN, VIN, vulva

Timeframe: No time limits were set on the search

Records identified: n= 566 + additional articles requested by WG members
Records referenced: n= 67

APPENDIX

WG2: Squamous Intraepithelial Lesions
Cervix, Vagina, Vulva, Penis, Anus, Perianus and Scrotum

WG2 Scope/Overall Purpose:

- To integrate current knowledge of the biology of HPV related processes with histopathologic terminology across all lower anogenital body sites
- To determine the potential tiering of terminology integrated with clinical utility
- To determine the best pathways to communicate to clinicians in a clear and relevant fashion
- To focus on clinical input – how the histopathologic diagnosis is reconciled with current clinical management
- To make recommendations for new unified terminology if appropriate

Key Questions (WG2 Charge):

1. What is the current state of clinical management based on the morphologic diagnosis? (In conjunction with WG 1)
2. What are the areas of potential overlap in histopathologic terminology (cytology, dermatopathology, GYN pathology)? (In conjunction with WG1)
3. What are the possibilities of integrating cytology, histology, molecular and clinical terminology? (molecular issues in conjunction with WG4)
4. Based on the possibilities, what would be recommended to clarify the histopathologic terminology?
5. Based on the recommendations, what are the criteria that define the histopathologic diagnosis?

WG2 Search Terms: Adenocarcinoma, anal, anal canal, anus, Anus Neoplasms, Bowenoid dysplasia, Bowenoid papulosis, Bowen's disease, carcinoma in situ, Carcinoma, Adenosquamous, carcinoma, squamous cell, cervical, Cervical Intraepithelial Neoplasia, cervix, cervix uteri, CIN, Epidemiologic Research Design, Erythroplasia of Queyrat, genital, HPV, Human papillomavirus, interobserver, intraepithelial neoplasia, intraobserver, Observer Variation, Papillomaviridae. , penile, Penile Diseases, Penile Neoplasms, penis, Perianal Intraepithelial Neoplasia, peri-anus, PIN 3, reliability, Reproducibility of Results, Sensitivity and Specificity, squamous, Uterine Cervical Dysplasia, Uterine Cervical Neoplasms, vagina, Vaginal Neoplasms, VaIN, VIN, vulva

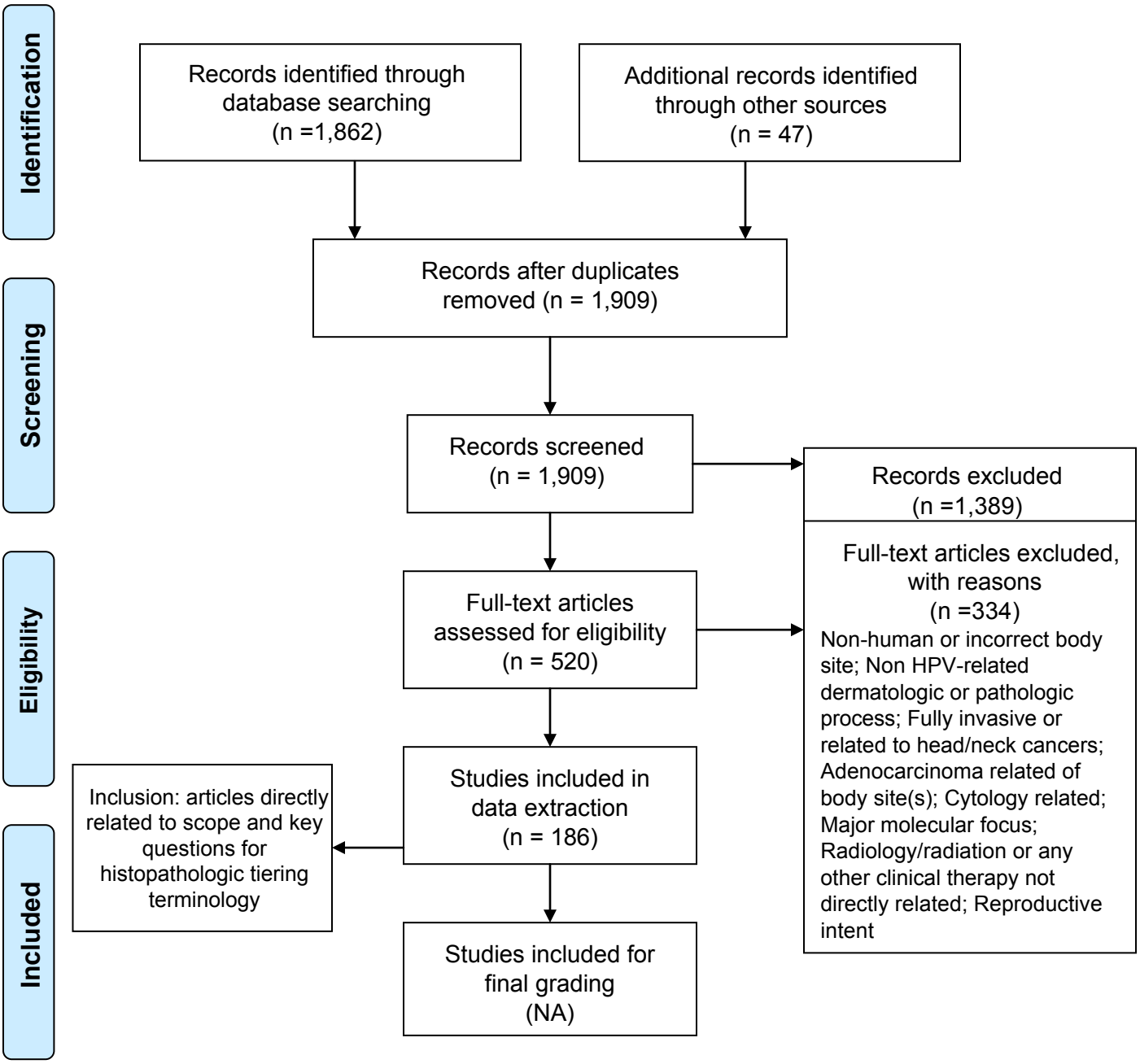
Timeframe: 1970 to current plus additional articles requested by WG members

APPENDIX

Literature Review Flow Diagram*

WG2: Squamous Intraepithelial Lesions

Cervix, Vagina, Vulva, Penis, Anus, Perianus and Scrotum



*Adapted with permission from Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS medicine*. 2009;6:e1000097.

APPENDIX

WG3: Superficially Invasive Squamous Cell Carcinoma Cervix, Vagina, Vulva, Penis, Anus, Perianus and Scrotum

WG3 Scope/Overall Purpose:

- To provide definitions in current usage by lower anogenital body sites (in conjunction with WG 1)
- To include definitions of minimally invasive cancers (e.g. micro-invasive, minimally invasive, early invasive, and superficially invasive) and carcinoma in general integrated with clinical utility
- To review data across sites to recommend specific terminology for minimally invasive cancers, especially where it is not well defined (i.e., anus)
- To provide best pathways to communicate to clinicians in a clear and relevant fashion
- To focus on clinical input – how the histopathologic diagnosis is reconciled with current clinical management
- To make recommendations for new unified terminology if appropriate

Key Questions (WG3 Charge):

1. What is the current state of clinical management based on the morphologic diagnosis? *(In conjunction with by WG 1)*
2. What are the areas of potential overlap in histopathologic terminology (cytology, dermatopathology, GYN pathology)? *(In conjunction with WG1)*
3. What are the possibilities of integrating cytology, histology, molecular and clinical terminology? (molecular in conjunction with WG4)
4. Based on the possibilities, what would be recommended to clarify the histopathologic terminology?
5. Based on the recommendations, what are the criteria that define the histopathologic diagnosis?
6. Based on the criteria, what are the differences that effect clinical management that the clinicians need to know?

WG3 Search Terms: anal, anal canal, anus, Anus Neoplasms, Bowenoid dysplasia, Bowenoid papulosis, Bowen's disease, carcinoma in situ, carcinoma, squamous cell, cervical, Cervical Intraepithelial Neoplasia, cervix, cervix uteri, CIN, early invasion, Erythroplasia of Queyrat, FIGO, genital, HPV, Human papillomavirus, intraepithelial neoplasia, Microinvasion, minimally invasive, penile, Penile Diseases, Penile Neoplasms, penis, Perianal Intraepithelial Neoplasia, peri-anus, PIN 3, Predictive Value of Tests, squamous, superficial, Uterine Cervical Dysplasia, Uterine Cervical Neoplasms, vagina, Vaginal Neoplasms, VAIN, VIN, vulva

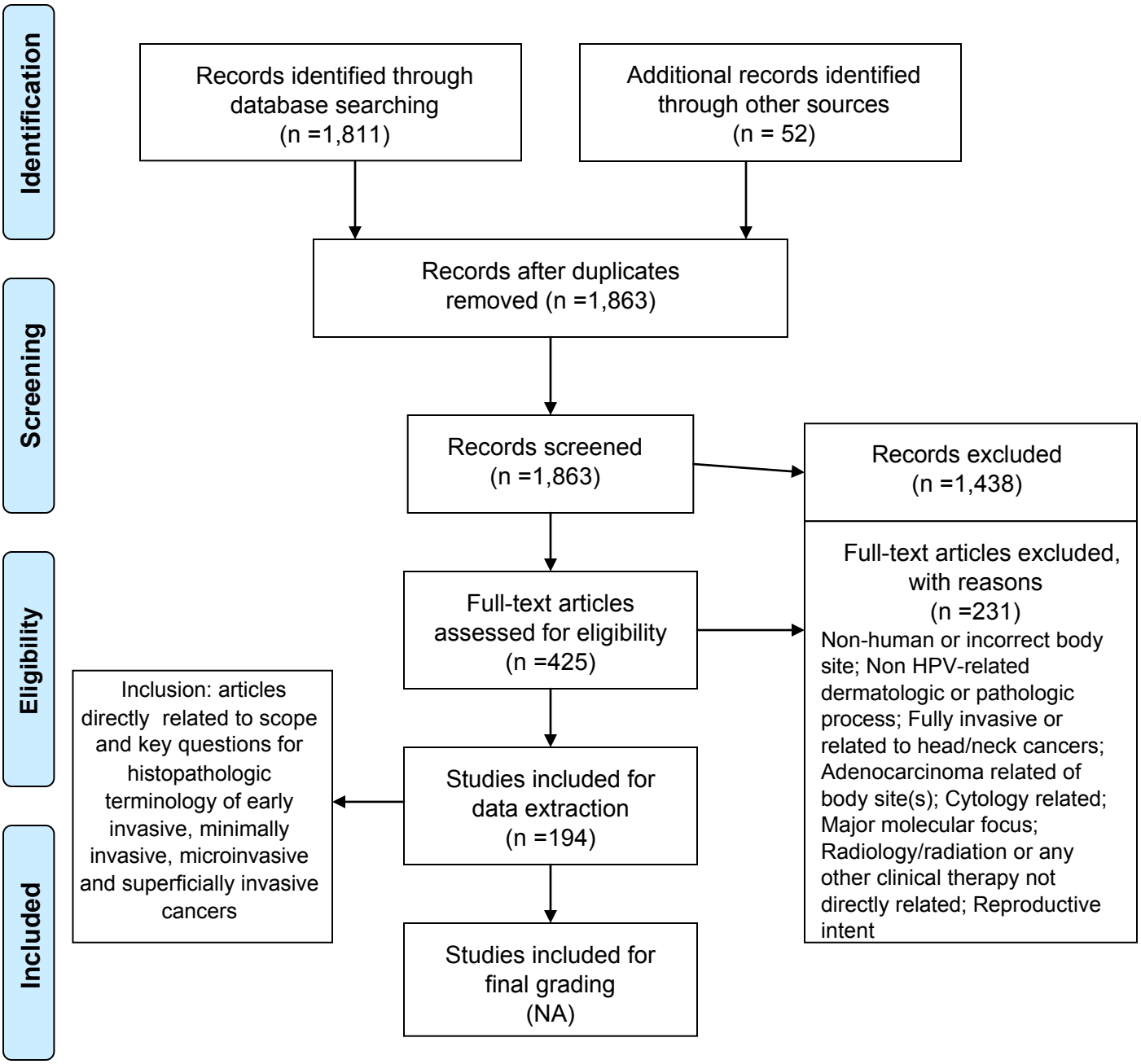
Timeframe: 1970 to current plus additional articles requested by WG members

APPENDIX

Literature Review Flow Diagram*

WG3: Superficially Invasive Squamous Cell Carcinoma

Cervix, Vagina, Vulva, Penis, Anus, Perianus and Scrotum



*Adapted with permission from Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS medicine*. 2009;6:e1000097.

APPENDIX

WG4: Biomarkers in HPV-associated Lower Anogenital Squamous Lesions Cervix, Vagina, Vulva, Penis, Anus, Perianus and Scrotum

WG4 Scope/Overall Purpose:

- To address definitions of histopathologic terminology for lower anogenital lesions across body sites by incorporating molecular markers
- To determine if there should be recommendations for use of molecular markers, and if interpretation guidelines should be created to reduce interobserver variability
- To recommend panels of immunostains/molecular tests by different diagnoses (e.g., high grade vs. reactive/immature metaplasia and/or atrophy), if appropriate
- To make recommendations for new unified terminology if appropriate

Key Questions (WG4 Charge):

1. What molecular markers (if any) are reported in the lower anogenital tract literature. Is any marker(s) ready for primetime use? If so, should such marker(s) be used to clarify diagnostic issues?
2. Can interobserver variability in the interpretation of lower anogenital lesions be reduced based on use of molecular markers?
3. Regarding the interpretation of equivocal lesional pathology, does the weight of evidence support use of molecular markers to increase sensitivity of diagnosis, and if so should molecular marker(s) be used on all specimens or just those in which the pathologist is considering a differential diagnosis?
4. What are the recommendations to clarify the histologic terminology, based on molecular marker input (in conjunction with WG 2 and WG 3)?
5. For low grade versus precancerous disease (-IN1 vs. -IN 2/3), will any marker positivity be definitional for precancer?
6. In making a determination of -IN 1 vs. no -IN, does p16 perform in supporting a diagnosis of any -IN?
7. Are there any prognostic markers of value, and if so, what are they?
    a. Does low-grade disease (-IN 1) with p16 staining (positive or negative) need to be managed differently from current practice?
8. For those studies involving multiple markers, is a combination of markers equivalent or better than a single marker?

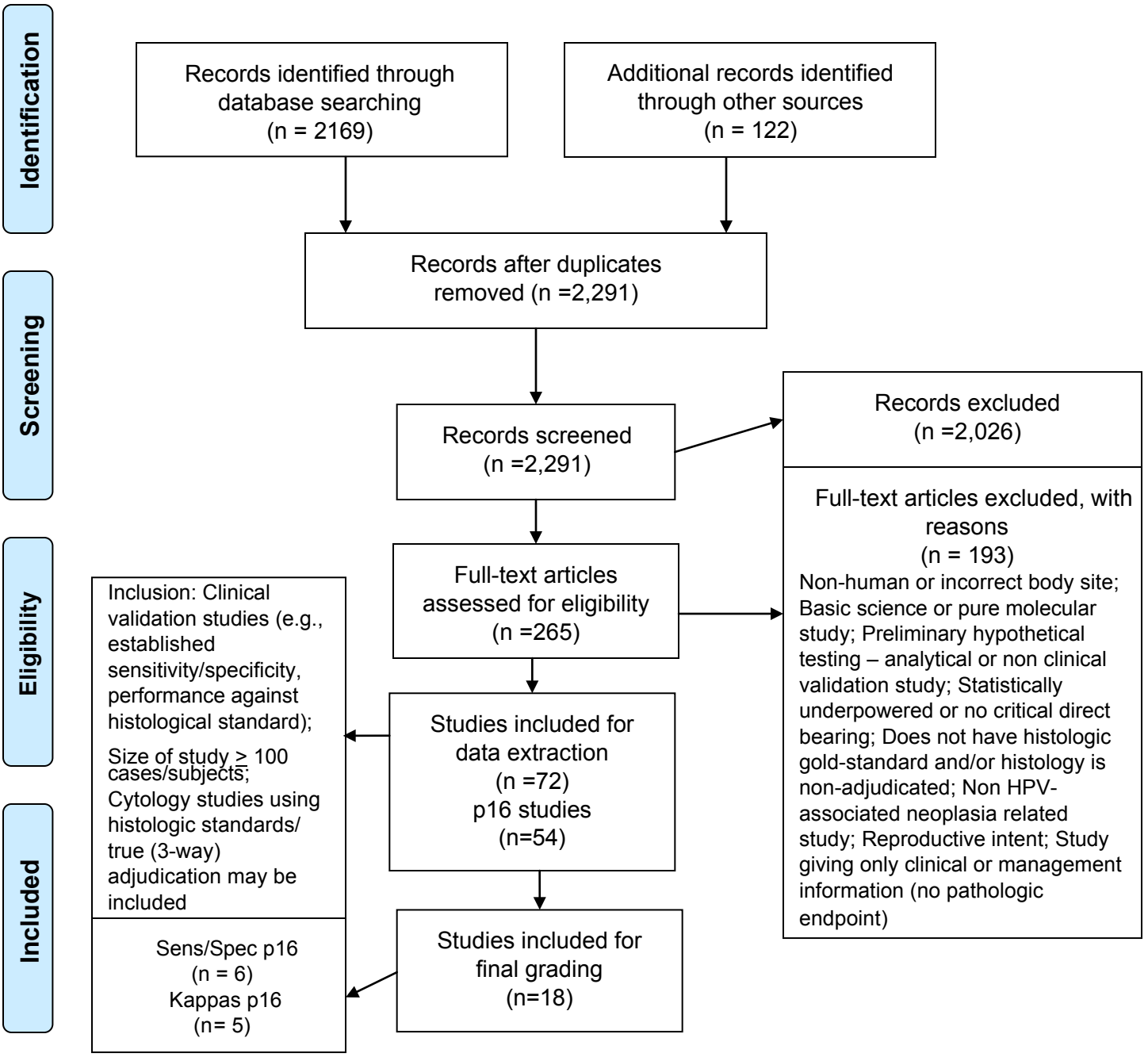
WG4 Search Terms: 3q26, anal, anal canal, anus, Anus Neoplasms, carcinoma in situ, carcinoma, squamous cell, CDKN2A, cervical, Cervical Intraepithelial Neoplasia, cervix, cervix uteri, CIN, Cyclin E, Cyclin-Dependent Kinase Inhibitor p16, DNA topoisomerase II alpha, DNA Topoisomerases, Type II, E6 messenger RNA, E6 mRNA, E7 messenger RNA, E7 mRNA, genital, HPV L1 protein, Human papillomavirus, INK4, intraepithelial neoplasia, Ki- 67, Ki-67 Antigen, L1, MCM, MCM2 protein, human, MIB1, MIB-1, MIB1 protein, human, p16, p16INK4a, Papillomavirus E7 Proteins., penile, Penile Diseases, Penile Neoplasms, penis, Perianal Intraepithelial Neoplasia, peri-anus, PIN 3, ProEx, RNA, Messenger, squamous, telomerase, telomerase RNA, TERC, TERT, TOP2A, topoisomerase II alpha, Uterine Cervical Dysplasia, Uterine Cervical Neoplasms, vagina, Vaginal Neoplasms, VaIN, VIN, vulva.

Timeframe: 1985 to current plus additional articles requested by WG members

APPENDIX

Literature Review Flow Diagram*

WG4: Biomarkers in HPV-associated Lower Anogenital Squamous Lesions Cervix, Vagina, Vulva, Penis, Anus, Perianus and Scrotum



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APPENDIX

WG5 Implications and Implementation of Standardized Terminology

WG5 Scope/Overall Purpose:

- To address the potential implications to the following areas:−
  Government/Regulatory/Nomenclature agencies
  - − Centers for Medicare and Medicaid Services (CMS), Joint Commission, American Joint Committee on Cancer (AJCC), International Federation of Gynecology and Obstetrics (FIGO), Society of Gynecologic Oncologists (SGO), World Health Organization (WHO), etc.
  - − Public Health/Research/Surveillance organizations
    - − Centers for Disease Control and Prevention (CDC), Surveillance Epidemiology and End Results (SEER), tumor registries
  - − Educational/Training/Testing organizations
    - − Specialty societies, training facilities, examination boards, publications and scientific literature
  - − Payers
    - − Current Procedural Terminology (CPT) and International Classification of Diseases (ICD) coding

- To develop action plans to implement the terminology
  - − Guideline publication
  - − Commentaries in other journals
  - − Presentations at national and international scientific meetings
  - − Coordination with clinical management guidelines [American Society for Colposcopy and Cervical Pathology (ASCCP), American Congress of Obstetricians and Gynecologists (ACOG)]
  - − Educational resources for health care professionals and patients
  - − Educational website- images, sample reports, etc
  - − Mobile apps
  - − Address laboratory accreditation checklists, tumor staging summaries
  - − Address billing issues and data collection

Key Questions (WG5 Charge):

1. What are the potential implications of standardizing histopathology terminology for lower anogenital lesions?
2. What is needed for successful implementation and dissemination of the terminology?
3. What is the strategy to inform clinicians of clinical implications of new standardized terminology, if any?