CINtec® Histology
Interpretation guide for immunohistochemistry staining of cervical punch biopsy specimens
Introduction

The CINtec® Histology antibody, anti-p16INK4a (clone E6H4), binds to the human cellular protein p16INK4a (p16). As a cyclin-dependent kinase inhibitor, p16 plays a key role in cell cycle regulation and cellular differentiation.1,2 The p16 protein controls the retinoblastoma protein (pRB)-mediated G1-S phase transition and triggers cell cycle arrest in the course of the cellular differentiation process.3 In normal, terminally differentiated cells, p16 is expressed at low levels typically not detectable by immunohistochemistry (IHC).1,4 Research studies have identified strong overexpression of p16 in precancerous and cancerous tissues to be closely linked to the expression of the human papillomavirus (HPV) E7 oncoprotein.1,7,8

IHC detection of p16 overexpression may aid in the interpretation of cervical histology specimens. The p16 protein has been reported to be over-expressed in squamous neoplastic epithelial lesions of the cervix uteri, whereas it has been found to be mostly absent in normal epithelium and non-neoplastic lesions.1,5,8 Numerous studies have investigated the correlation between p16 overexpression and the presence of cervical intraepithelial neoplasia (CIN).9,10 Overexpression of p16 has been observed in virtually all CIN3 lesions, the vast majority of CIN2 lesions, and typically within 40% to 60% of squamous cervical lesions classified as CIN1 in Hematoxylin and Eosin (H&E) stained tissue sections.9,11-13

Diagnostic interpretation of cervical biopsy specimens establishes the basis for patient treatment decisions. CIN1 is the histologic manifestation of an HPV infection. In general, it is recommended that patients diagnosed with CIN1 lesions return for follow-up evaluation in 1 year.14 For cervical disease, CIN2 is the most commonly used clinical threshold for treatment.14 Excisional or ablative therapy is recommended for patients diagnosed with CIN2 or CIN3. The risk of excisional treatment to the patient of child-bearing age includes adverse effects on future pregnancies.15-17 Therefore, accurate diagnosis of CIN and in particular CIN2 and CIN3 is important in patient management decisions.18

Morphological interpretation of cervical biopsy specimens by H&E alone is subject to interobserver variability.18-24 Several studies have evaluated the adjunctive use of p16-stained slides and the effect on interobserver reliability in diagnostic interpretation of cervical histology specimens by pathologists. In all of these studies, the diagnostic agreement between pathologists improved significantly when p16-stained slides were interpreted along with H&E-stained slides compared to interpretation of the H&E-stained slide alone.11,12,21,25-27

Furthermore, several studies assessed the effect on diagnostic accuracy of cervical histology interpretation when p16-stained slides were used along with H&E-stained slides. Dijkstra and colleagues (2010) showed an almost perfect agreement between diagnoses established with support of p16-stained slides interpreted by a single pathologist compared to the adjudicated diagnoses made by an expert pathologist panel based on H&E staining only.12 Bergeron and colleagues (2010) reported a significant increase in diagnostic accuracy when interpretation included both p16-stained slides and H&E-stained slides compared with H&E-stained slide interpretation alone (p=0.0004), with sensitivity for CIN2+ increasing from 77% to 87%.12 In a recent prospective, population-based study in which an academic clinical center in the U.S. analyzed more than 1,450 consecutive cervical biopsy cases, staining for p16 was found "to be a useful and reliable diagnostic adjunct for distinguishing biopsies with and without CIN2+."12 Therefore, the adjunctive interpretation of H&E-stained slides comprising cervical biopsy sections together with consecutive slides from the same tissue specimen immunostained for p16 has the potential to significantly improve diagnostic agreement in the interpretation of cervical biopsies.

In 2012, the College of American Pathologists (CAP) and the American Society for Colposcopy and Cervical Pathology (ASCCP) issued the Lower Anogenital Squamous Terminology (LAST) recommendations.25 The LAST recommendations provide guidance for clinical use of p16 IHC along with H&E to improve the detection of HPV-associated pre-cancerous lesions within cervical (and other lower anogenital tract) squamous tissues in specific circumstances. The use of p16 IHC is recommended when: 1) the H&E morphologic differential diagnosis is between pre-cancer (CIN2 or CIN3) and a mimic of pre-cancer; 2) the H&E morphologic diagnosis is CIN2; 3) the H&E morphologic diagnosis is ≤CIN1 and the biopsy specimen is at high risk for missed high-grade disease, which is defined as prior cytologic interpretation of HSIL (high-grade squamous intraepithelial lesion), ASC-H (atypical squamous cells, cannot rule out high-grade squamous intraepithelial lesion), ASC-US/HPV16+ (atypical squamous cells of undetermined significance/HPV16+), or AGC-(NOS) (atypical glandular cells- not otherwise specified); or 4) in the case of professional disagreement in histological diagnosis, particularly if the differential diagnosis includes a CIN2 or CIN3 pre-cancerous lesion. In 2014, the World Health Organization (WHO) adopted the LAST consensus recommendations; the adjunctive use of p16 IHC in evaluation of cervical biopsies is now considered recommended standard of care.29
Intended Use

CINtec® Histology is a qualitative immunohistochemistry (IHC) test using mouse monoclonal anti-p16 antibody clone E6H4, and is intended for use in the light microscopic assessment of the p16INK4a protein in formalin-fixed, paraffin-embedded (FFPE) cervical punch biopsy tissues using OptiView DAB IHC Detection Kit on a VENTANA BenchMark ULTRA instrument.

The test is indicated as an adjunct to examination of hematoxylin and eosin (H&E) stained slide(s), to improve consistency in the diagnosis of cervical intraepithelial neoplasia (CIN). Diagnosis of CIN presence or level should be based on H&E stained slide(s) and other clinical and laboratory test information.

Intended for in vitro diagnostic (IVD) use. Prescription Use Only.

Purpose of Interpretation Guide

This guide is intended to:

- Provide pathologists with a tool to facilitate clinical evaluation of formalin-fixed, paraffin-embedded cervical biopsy sections stained with the CINtec Histology assay using the interpretation of the CINtec Histology status along with morphologic H&E interpretation of the specimen.
- Provide photographic images that illustrate the p16 staining patterns that may result from staining cervical biopsy specimens with the CINtec Histology assay.
- Provide a reference for interpreting CINtec Histology-stained specimens according to a binary rating system (“positive” or “negative”).
- Provide case examples demonstrating specific use and interpretation of CINtec Histology.
Clinical Evaluation – p16 Staining Patterns

The CINtec Histology assay is designed to be used on formalin-fixed, paraffin-embedded punch biopsy specimens collected from the cervix uteri. The CINtec Histology test identifies over-expression of the p16 protein. CINtec Histology is a qualitative test and the CINtec Histology status is interpreted as either positive or negative based on the p16 staining pattern in the cervical squamous epithelium. Positive CINtec Histology status is identified by diffuse p16 staining. Negative CINtec Histology status is identified by either focal p16 staining, or no p16 staining. The interpretation of the CINtec Histology status and p16 staining patterns within the cervical squamous epithelium are described in more detail in the following sections.

Positive CINtec Histology status

Positive CINtec Histology status is defined as diffuse, continuous staining of cells of the basal and parabasal cell layers of the cervical squamous epithelium, with or without staining of the intermediate or intermediate to superficial cell layers (referred to as “diffuse”). The p16 staining intensity can vary between specimens. Diffuse immunostaining specific for p16 of any intensity is considered to be positive for CINtec Histology status. Cellular p16 staining for CINtec Histology may be nuclear and/or cytoplasmic.

As shown in Figure 1, diffuse p16 staining begins with the continuous staining of the basal and parabasal cell layers and can extend to the full thickness of the epithelium or it may involve variable amounts of the epithelium (e.g. the lower third, lower half, or two thirds).

Figure 1. Diffuse p16 staining (positive CINtec Histology status).
Diffuse staining demonstrates a continuous staining pattern of the basal and parabasal cell layers with or without the staining of the intermediate or intermediate to superficial cell layers as shown below in the images of CIN lesions (Figure 2).

Figure 2. Positive CINtec Histology status: CINtec Histology-stained case examples showing diffuse p16 staining. Final CIN diagnosis for each case is based on the respective H&E-stained slide (not shown).

NOTE:  p16 staining intensity and the presence of a diffuse p16 staining pattern cannot be used for grading a CIN lesion. The proportion of cervical epithelium staining (i.e. staining from the basal cell layer up to full thickness) does not correlate with the CIN grade. The vast majority of high-grade CIN lesions will demonstrate a diffuse p16 staining pattern, and typically 40 to 60% of CIN1 lesions may demonstrate the diffuse pattern. Diffuse staining suggests the presence of CIN. Routine morphological criteria on the H&E stained slide must be used to grade the case as CIN1, 2, or 3.

Negative CINtec Histology status

Negative CINtec Histology status is defined as either focal p16 staining of the cervical squamous epithelium (“focal p16 staining” as shown in Figure 3 and Figure 4) or no p16 staining in the cervical squamous epithelium (“no p16 staining” as shown in Figure 3 and Figure 5). Focal p16 staining is defined as staining of isolated cells or small cell clusters; i.e. a non-continuous staining pattern, particularly not of the basal and parabasal cells. In Figure 3, the left panel shows focal p16 staining representative of negative CINtec Histology status. A few p16 positive cells are scattered throughout the epithelium, and there is no continuous staining of epithelial cells, and especially not comprising basal/parabasal cell layers.

Figure 3. Focal p16 staining (left panel) and no p16 staining (right panel). Both of these p16 staining patterns are representative of negative CINtec Histology status.
**Clinical Evaluation – CINtec Histology Use in Clinical Practice**

The recommended use of CINtec Histology requires serial sections from each case: one or more serial sections for hematoxylin and eosin (H&E) staining, a serial tissue section for CINtec Histology staining, and a serial tissue section for a negative reagent control. It is recommended that known positive and negative tissue control specimens be used on the CINtec Histology-stained patient tissue slide (refer to section: Use of Controls – Negative Reagent Control and Tissue Controls).

For each sample, the H&E-stained slide(s) should first be reviewed to establish an initial diagnosis. A corresponding slide stained with a negative reagent control may then be reviewed to evaluate nonspecific background staining. Next, the slide stained with CINtec Histology should be evaluated. The positive and negative tissue control specimens on the CINtec Histology-stained slide should be examined to confirm the staining is acceptable. The patient specimen is subsequently interpreted as either positive for CINtec Histology (diffuse p16 staining pattern) or negative for CINtec Histology (focal p16 staining pattern or no p16 staining). The p16 staining pattern may either confirm the initial H&E impression or it may not support it. After review of the CINtec Histology-stained slide, final diagnosis of the patient specimen is based on the routine morphological assessment of the H&E-stained slide(s) to establish CIN grade (CIN 1, CIN 2 or CIN 3) or rating the specimen as negative for CIN/dysplasia.

Figure 6 provides a general flowchart that outlines how the CINtec Histology test should be interpreted. If there are no p16 positive cells present within the epithelium, the CINtec Histology status is negative. If p16 positive cells are present, the staining pattern should then be classified as diffuse or focal. Only a diffuse p16 staining pattern within the cervical squamous epithelium is considered as positive CINtec Histology status.
Figure 6. Cervical biopsy interpretation flowchart.
Interpretation of CINtec Histology - Important Criteria

The CINtec Histology test may serve as a “locator tool” by highlighting CIN lesions that may not have been identified on the initial review of the H&E-stained slide. In addition, the CINtec Histology test may help in the differential diagnosis when a suspicious area is identified on the H&E-stained specimen. If the region of interest shows positive CINtec Histology status, a diagnosis of CIN1, CIN2 or CIN3 should be considered. Since the vast majority of high-grade CIN lesions demonstrate a diffuse p16 staining pattern, specimens showing negative CINtec Histology status may not support a high-grade CIN diagnosis. However, an occasional high-grade case that shows negative CINtec Histology status may be encountered. The CINtec Histology status does not overrule the H&E-based diagnosis; it compliments it. Final diagnosis of the patient specimen is based on the H&E-stained slide interpretation taking into account the CINtec Histology-stained slide results along with any additional clinical information.

CIN1 lesions may demonstrate any p16 staining pattern

It is important to note that CIN1 lesions may demonstrate any p16 staining pattern. They may demonstrate no p16 staining, focal p16 staining, or diffuse p16 staining.

![No p16 staining](image1.png) ![Focal p16 staining pattern](image2.png) ![Diffuse p16 staining pattern](image3.png)

Figure 7. CINtec Histology-stained CIN1 lesions can demonstrate the full range of staining patterns: no p16 staining (left panel), focal p16 staining pattern (center panel), or diffuse p16 staining pattern (right panel). Final CIN diagnosis is based on the respective H&E-stained slide (not shown).
Full thickness diffuse staining is not necessarily an indicator of high-grade CIN

In various studies, 40% to 60% of CIN1 lesions were found to be diffusely positive. Furthermore, the diffuse p16 staining pattern in CIN1 lesions may involve variable amounts of the epithelium (e.g. only the lower third, lower half, two thirds or full thickness). Full thickness staining of the epithelium is not an indicator of high-grade CIN. Routine morphological criteria on the H&E-stained slide must be used to grade the lesion as CIN1, CIN2, or CIN3.

Figure 8. CINtec Histology-stained CIN1 case examples showing diffuse p16 staining patterns in the basal lower third to one half (left panel and center panel) and full thickness diffuse p16 staining (right panel). Each of these cases demonstrate positive CINtec Histology status. Final diagnosis of the case is based on the H&E morphology.

p16 Staining is nuclear and/or cytoplasmic

The subcellular localization of p16 protein is not considered in interpreting the staining result. Cells displaying either nuclear and/or cytoplasmic staining are considered positive for p16 overexpression. Most often, combined nuclear and cytoplasmic staining will be seen.

Figure 9. Cervical punch biopsy showing a diffuse p16 staining pattern; most of the basal and parabasal cell layers have both nuclear and cytoplasmic staining. However, higher up in the epithelium some cells demonstrate only nuclear staining and others cells demonstrate solely cytoplasmic staining.
Staining intensity plays no role in interpretation of the p16 stain

Staining intensity plays no role in interpretation of the p16 stain. Typically, a large portion of diffusely stained lesions will stain dark brown; but in some cases, the p16 stain may be less intense, or there may be a gradient with darker staining of the basal and parabasal cell layers and progressively lighter p16 staining in the intermediate or intermediate to superficial cell layers.

Figure 10. Cervical punch biopsy showing a less intense, diffuse p16 staining pattern (left panel). Cervical punch biopsy showing diffuse p16 staining (right panel). Both tissue section images show darker staining of the basal and parabasal cell layers with a progressively lighter gradient in the intermediate and intermediate to superficial cell layers.

CINtec Histology Staining Not Taken into Account in Interpretation

Stromal cell staining

CINtec Histology will occasionally stain stromal cells. The interpretation of the CINtec Histology test is specific to the squamous epithelium. Therefore, staining of stromal cells is not taken into account when interpreting the p16 stain. Figure 11 shows an example of stromal cell staining underneath a diffusely staining cervical squamous epithelial lesion. In some cases stromal cells may demonstrate intense nuclear and/or cytoplasmic staining. Nevertheless, staining of stromal cells is not taken into account in the interpretation.

Figure 11. Cervical punch biopsy showing stromal cell staining underneath a diffuse staining cervical lesion (right panel, CINtec Histology-stained slide). Stromal cells are indicated by the arrows. Stromal cell staining is not evaluated in determining CINtec Histology status.
Endocervical cell staining

It is not uncommon for the glandular epithelium (or endocervical cells) to stain intensely. Figure 12 shows a case with p16 staining within endocervical epithelial tissue. p16 expression in the glandular epithelium (or within endocervical cells) is not evaluated. Interpretation of the p16 staining pattern is based on the staining within the cervical squamous epithelium only.

**Figure 12.** Cervical punch biopsy showing p16 staining within endocervical cells (right panel, CINtec Histology-stained slide). Endocervical cell staining is not evaluated in determining CINtec Histology status.

Background Staining

Mucus and/or chromogen trapping may occasionally be observed in some specimens. In addition, it is not uncommon for trapping to be observed in a negative reagent control-stained slide or in a CINtec Histology-stained slide (Figure 13). These types of background staining should be ignored when interpreting the CINtec Histology status of the patient specimen.

**Figure 13.** Cervical punch biopsy showing chromogen trapping within the lower portion of the tissue (center panel, negative reagent control-stained slide, and right panel, CINtec Histology-stained slide). Some mucus and endocervical gland staining is also evident (right panel, CINtec Histology-stained slide).
Use of Controls – Negative Reagent Control and Tissue Controls

Negative reagent control

It is strongly recommended that a negative reagent control be used to stain an adjacent section of the patient specimen tissue on a separate slide from the CINtec Histology-stained slide. The staining protocol used for a negative reagent control antibody should be the same as that for the CINtec Histology antibody.

When using a negative reagent control-stained slide, compare any observed staining to the CINtec Histology-stained slide. Intact cells should be used for interpretation of negative reagent control staining results, as necrotic or degenerated cells often stain nonspecifically. However, the majority of cases will demonstrate little to no background staining using a negative reagent control. If the CINtec Histology-stained slide and the negative reagent control-stained slide have comparable staining, then that staining cannot be specific for p16.

![Figure 14. High-grade CIN case showing acceptable staining of a negative reagent control (center panel).](image)

**Positive and negative tissue controls**

It is strongly recommended to use positive and negative tissue controls on the same slide as the patient tissue specimen when staining with CINtec Histology. Positive CINtec Histology status and negative CINtec Histology status tissue controls should be fixed and processed in the same manner as the patient specimen. The known positive and negative tissue controls are used only to monitor the steps of specimen processing and proper function of the reagents and instrument within the staining run.

For optimal quality control, CIN2, CIN3, or cervical carcinoma tissue of known positive p16 immunostaining is suitable for use as a positive tissue control; normal cervical tissue negative for p16 staining is suitable for use as a negative tissue control. Criteria for evaluation are described in Table 1 below.

Alternatively, normal human tonsil tissue is suitable for use as a tissue control. Tonsil contains both positive and negative staining elements for p16 staining with CINtec Histology. Within normal tonsil tissue, there is nuclear and/or cytoplasmic staining of scattered squamous epithelial cells primarily in crypt epithelium and scattered follicular dendritic cells in germinal centers and absence of staining in the majority of lymphocytes (rare staining lymphocytes may be observed).

Control tissue should be biopsy or surgical specimens prepared and fixed in a manner identical to the test specimen. Such tissue may be used to monitor all steps from tissue preparation through staining.
**Table 1. Evaluation Criteria for CINtec Histology-stained Cervical Tissue Controls**

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<th>Tissue Controls</th>
<th>Acceptable</th>
<th>Unacceptable</th>
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<tr>
<td>CIN2, CIN3, or cervical carcinoma</td>
<td><strong>CIN2 or CIN3 tissue control:</strong> diffuse continuous staining of cells of the basal and parabasal cell layers of the cervical squamous epithelium, with or without staining of cells of the intermediate, or intermediate to superficial cell layers</td>
<td><strong>CIN2 or CIN3 tissue control:</strong> no staining observed with CINtec Histology or staining of isolated cells or small cell clusters (i.e. non-continuous staining, particularly not of the basal and parabasal cell layers)</td>
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<td></td>
<td><strong>Cervical carcinoma tissue control:</strong> diffuse continuous staining of invasive carcinoma</td>
<td><strong>Cervical carcinoma tissue control:</strong> no staining observed with CINtec Histology or staining of isolated cells or small cell clusters within the invasive carcinoma</td>
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<tr>
<td>Normal cervical squamous epithelium</td>
<td>Either a negative staining reaction or a staining of isolated cells or small cell clusters, (i.e. non-continuous staining, particularly not of the basal and parabasal cell layers)</td>
<td>Diffuse continuous staining of cells of the basal and parabasal cell layers of the cervical squamous epithelium, with or without staining of cells of the intermediate, or intermediate to superficial cell layers</td>
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**Case examples**

**Inflammation**

*Figure 15. Negative CINtec Histology status:* This cervical punch biopsy shows some inflammation; there are neutrophils within the epithelium and plasma cells and lymphocytes within the underlying stroma (left panel, H&E-stained slide). The CINtec Histology-stained slide (right panel) shows focal p16 staining that is most pronounced in the intermediate and superficial epithelial cell layers. There are a few darkly stained single cells, some cells with moderate staining intensity and some cells with light staining intensity. The basal and parabasal cells are not involved.

**Squamous metaplasia**

*Figure 16. Negative CINtec Histology status:* Squamous metaplasia in an area of inflammation (left panel, H&E-stained slide) showing no p16 staining (right panel, CINtec Histology-stained slide).
Figure 17. **Negative CINtec Histology status:** Squamous metaplasia (left panel, H&E-stained slide) showing a focal p16 staining pattern (right panel, CINtec Histology-stained slide). There are small cell clusters staining throughout the epithelium.

Figure 18. **Negative CINtec Histology status:** Squamous metaplasia (left panel, H&E-stained slide) showing a focal 16 staining pattern (right panel, CINtec Histology-stained slide).

**Condyloma**

Figure 19. **Negative CINtec Histology status:** Condyloma (left panel, H&E-stained slide) showing a focal p16 staining pattern (right panel, CINtec Histology-stained slide). There is focal p16 staining observed as mostly single cells and small cell clusters scattered through the epithelium.
Figure 20. **Negative CINtec Histology status:** CIN1 (left panel, H&E-stained slide) showing koilocytosis that is clearly evident in the superficial epithelium. The CINtec Histology-stained slide shows no p16 staining (right panel). Chromogen trapping is observed below the squamous epithelium in both the negative reagent control-stained slide (center panel) and the CINtec Histology-stained slide.

Figure 21. **Negative CINtec Histology status:** CIN1 (left panel, H&E-stained slide) showing a focal p16 staining pattern (right panel, CINtec Histology-stained slide). There are several darkly staining single cells and some lighter staining cells throughout the epithelium. The basal and parabasal cells are uninvolved.

Figure 22. **Positive CINtec Histology status:** CIN1 (left panel, H&E-stained slide) showing diffuse, continuous staining in the lower third of the epithelium (right panel, CINtec Histology-stained slide).
Positive CINtec Histology status: CIN1 (left panel, H&E-stained slide) showing a diffuse p16 staining pattern (right panel, CINtec Histology-stained slide). The portion of the epithelium staining varies and approaches full thickness in some areas. This particular case is lighter in intensity; but staining intensity plays no role in evaluation of the CINtec Histology status.

Figure 23.

Positive CINtec Histology status: CIN1 (left panel, H&E-stained slide) showing a diffuse p16 staining pattern involving the full thickness of the epithelium throughout the lesion (right panel, CINtec Histology-stained slide). The CINtec Histology-stained slide also highlights a stained endocervical gland.

Figure 24.

Positive CINtec Histology status: CIN2 (left panel, H&E-stained slide) showing some koilocytosis in the upper epithelium. The CINtec Histology-stained slide (right panel) shows diffuse p16 staining in the lesional area (positive CINtec Histology status). The diffuse p16 staining abruptly stops at the transition to normal epithelium.

Figure 25.
**Figure 26. Positive CINtec Histology status:** CIN2 (left panel, H&E-stained slide) showing full-thickness, diffuse p16 staining (right panel, CINtec Histology-stained slide).

**CIN 3**

**Figure 27. Positive CINtec Histology status:** CIN3 (left panel, H&E-stained slide) showing diffuse p16 staining (right panel, CINtec Histology-stained slide).

**Figure 28. Positive CINtec Histology status:** CIN3 (left panel, H&E-stained slide) showing diffuse p16 staining in the CINtec Histology-stained slide (right panel).
Small Lesions Highlighted by CINtec Histology

Figure 29. Positive CINtec Histology status: Small lesion: At 4x and 40x magnification, a small area of interest (arrow) shows diffuse p16 staining on the CINtec Histology-stained slide (top right panel and bottom right panel, respectively). Review of the H&E-stained slide at 40x magnification (bottom left panel) identifies this small lesion as CIN2. This lesion may have been missed by H&E alone.
**Figure 30. Positive CINtec Histology status:** Small lesion: At 10x magnification, this case shows chronic inflammation and reactive appearing changes within the squamous epithelium (top left panel, H&E-stained slide). CINtec Histology highlights a detached fragment of the epithelium with diffuse p16 staining (top right panel and bottom right panel, CINtec Histology-stained slide). Review of this fragment on the H&E-stained slide at 40x magnification (bottom left panel) identifies this lesion as CIN2.
Figure 31. **Positive CINtec Histology status:** Small lesion. At 4x and 40x magnification, a small area of interest shows diffuse p16 staining on the CINtec Histology-stained slide (top right panel and bottom right panel, respectively). Review of the H&E-stained slide at 40x magnification (bottom left panel) identifies this small lesion as CIN2. This lesion may have been missed by H&E alone.
References


