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Chapter 1
Overview
1.1 Introduction

Cervical carcinoma is the second most frequent cancer in women world-wide. In Europe, USA, Japan, however, due to efficient mass screening programs there is a marked difference in the incidence of cervical cancers and associated mortality rates. Since the introduction of population-wide mass screening with the cytological Papanicolaou’s test (Pap), the incidence of invasive cervical cancer has sharply declined. Despite this success, cytological screening with the Pap test has substantial limitations, mainly with regards to sensitivity, but in parts also with respect to specificity. The subjective nature of the morphological criteria used to identify and classify abnormal cells is one of the major reasons for these limitations of current Pap testing.

Extensive research over the past decades has provided strong evidence that persistent infections with high-risk types of Human Papilloma Viruses (HR-HPV) represent the major etiologic agent for cervical cancer. Depending on their age, however, more than 20% of women may be infected with the virus, and only very few may develop clinically relevant dysplastic lesions or even cancer.

During an acute HPV infection, the expression of viral genes, in particular the viral oncogenes E6 and E7, is restricted to differentiated epithelial cells that have lost their capability to replicate.

High-grade cervical dysplasia, however, is initiated by deregulated expression of viral oncogenes in replicating epithelial stem cells. Here, the E6-E7 gene products gain control of the cell cycle and the mitotic apparatus first and thus induce severe genetic instability, which is morphologically reflected mainly in an altered nuclear-cytoplasmic ratio, anisonucleosis and hyperchromasia.

The detailed molecular analysis of these activities allowed to identify a new biomarker over-expressed in dysplastic cervical cells. The over-expression of the cyclin-dependent kinase inhibitor p16INK4a (p16) in dysplastic cells indicates an active expression of the viral oncogene E7.

Despite the strong correlation between an active expression of the viral oncogene E7 and the over-expression of p16, there are some morphological features to be focused on while evaluating cervical cytology slides immuno-stained for p16 only, as p16 may be occasionally over-expressed as well in some non-dysplastic cell types, such as mature metaplastic cells.
Introduction, cont.

To further reduce the level of subjectivity that may be associated with the interpretation of the morphology of p16 immuno-reactive cells, mtm has included the detection of the well known proliferation marker Ki-67 as a second marker to the test that adds an so far unknown level of objectivity to the evaluation of cervical cytology specimens.

The Ki-67 protein is a cellular marker for proliferation. During interphase, the Ki-67 antigen can be exclusively detected within the cell nucleus. Ki-67 protein is present during all active phases of the cell cycle (G1, S, G2 and mitosis), but it is absent from resting cells (G0).

The immuno-histochemical detection of Ki-67 has developed into a standard reagent in the pathology laboratory to assess the proliferative activity of cancers. By determining the proliferation index, i.e. the proportion of Ki-67 positive cells within a tumor tissue, Ki-67 expression is widely used as a prognostic and a predictive marker in many cancer entities.

Quite often the term MIB-1 is used almost synonymously for the Ki-67 protein when referring to the evaluation of Ki-67 expression levels in human tissue samples. This is due to the fact that the MIB-1 antibody has been the first monoclonal antibody that detected the Ki-67 protein in formalin-fixed, paraffin-embedded tissue sections and is being widely used.
Under normal physiological conditions, p16 expression leads to a cell cycle arrest, which is a prerequisite for terminal differentiation. This means that in cells with an intact cell cycle regulation p16 when expressed has an anti-proliferative effect. This explains the sporadic physiological staining of e.g. individual mature squamous metaplastic cells and some glandular epithelial cells of the cervix.

1.2 Role of p16^{INK4a}
1.3 Role of Ki-67

The Ki-67 protein is strictly associated with cell proliferation and is expressed in proliferating cells within the nuclei. Physiologically it can be detected within the nucleus of e.g. parabasal cells of normal squamous epithelium.
1.4 Molecular Pathogenesis

Over-expression of p16 has been suggested to be a consequence of the functional inactivation of the retinoblastoma protein (pRb). In the case of cervical cancer and its precursor lesions, inactivation of pRb is mediated by the binding of the E7 oncoprotein of high-risk human papillomaviruses (HR-HPV) to pRb. Since expression of p16 underlies a negative feedback control through functional pRb, over-expression of p16 represents a useful biomarker for cervical intra-epithelial lesions where HR-HPV has started its transforming activity thru its E6 and E7 onco-proteins.

Due to the inactivation of pRb by the E7 onco-proteins, the normal anti-proliferative activity of p16 is abrogated in cervical intra-epithelial neoplasia. Cells where the transformation process mediated by the HR-HPV onco-proteins has started can proliferate despite high levels of functional p16 protein.
1.5 p16 Expression in Cervical Dysplasia

Dysplasia caused by HR-HPV

\text{p16}^\text{INK4a} immunostain: \textit{diffuse} distribution of positive cells in immature layers

Scheme of p16 immunostaining in dysplasia: gradual increase in p16 positivity with progression of dysplasia, starting from basal and parabasal cell layers.
1.6 The Concept of CINtec® PLUS

The simultaneous expression of the normally anti-proliferative protein p16 and a proliferation marker such as Ki-67 within the same epithelial cell should exclude each other. The detection of individual cervical epithelial cells co-expressing both markers thus may represent an indicator of cell-cycle deregulation.

The detection of cervical epithelial cells within cervical cytology preparations that show double immuno-reactivity for both p16 and Ki-67 after the simultaneous immuno-staining for both proteins using may be used as an approach to identify underlying cervical dysplasia.

The figures below show the simultaneous expression of p16 and Ki-67 in cervical intra-epithelial lesions when staining paraffin sections simultaneously for p16 and Ki-67.

The CINtec® PLUS Kit has been developed and validated for its use on alcohol-fixed cervical cytology preparations to detect the co-expression of the p16 and Ki-67 proteins within the same cervical cells.
1.7 Staining Principle

The CINtec® PLUS Kit is an immunocytochemistry assay for the simultaneous qualitative detection of the p16\(^{\text{INK4a}}\) and Ki-67 proteins in cervical cytology preparations. The ready-to-use reagent Kit is based on a primary antibody cocktail of p16\(^{\text{INK4a}}\) specific mouse monoclonal antibody (clone E6H4) and a Ki-67 specific rabbit monoclonal antibody, followed by two visualisation reagents (HRP and AP) and two different substrate-chromogens (DAB and Fast Red).
1.7 Staining Principle cont.

- **p16^INK4a**
  - Cytoplasm
  - Mouse anti-human 16^INK4a antibody (clone E6H4)
  - Rabbit anti-human Ki-67 antibody

- **Ki-67**
  - Nucleus
  - Anti-mouse HRP polymer
  - Anti-rabbit AP polymer
1.7 Staining Principle cont.

- **p16**
  - **INK4a**
  - **Ki-67**

**Cytoplasm**
- Mouse anti-human 16^{INK4a} antibody (clone E6H4)
- Rabbit anti-human Ki-67 antibody
- Anti-mouse HRP polymer
- Anti-rabbit AP polymer

**Nucleus**
- Mouse anti-human 16^{INK4a} antibody (clone E6H4)
- Rabbit anti-human Ki-67 antibody
- Anti-mouse HRP polymer
- Anti-rabbit AP polymer
1.7 Staining Principle

anti-mouse HRP polymer

mouse anti-human p16\textsuperscript{INK4a} antibody (clone E6H4)

rabbit anti-human Ki-67 antibody

cytoplasm

nucleus

anti-rabbit AP polymer

mouse anti-human p16\textsuperscript{INK4a} antibody (clone E6H4)

rabbit anti-human Ki-67 antibody

cytoplasm

nucleus
1.7 Staining Principle

- p16\textsuperscript{INK4a}
- cytoplasm
- Ki-67
- nucleus

![Image of stained cells with p16\textsuperscript{INK4a} and Ki-67 staining]
Single layered cells
2.1 Single Layered Cells
Description

1. Isolated individual dual-stained cells are easiest to identify as such

2. The brown cytoplasm and the red nucleus are clearly visible

3. Nucleus and cytoplasm can clearly be allocated to the same cell
   ➔ Confirm that nucleus and cytoplasm is in one plain

4. A positive CINtec® PLUS result is defined by the detection of one or more dual-stained cervical epithelial cell(s)
2.1 Single Layered Cells

CINtec® PLUS positive: Single-layered cell with brown cytoplasm and red nucleus.
Mat.: ThinPrep, LSIL  40x

CINtec® PLUS positive: 2 Single-layered cells, one with brown cytoplasm and red nucleus.
Mat.: ThinPrep, LSIL  40x
2.1 Single Layered Cells, cont.

CINtec® PLUS positive: Single-layered cell with brown cytoplasm and red nucleus. Mat.: ThinPrep, HSIL 40x

Note that sometimes the cytoplasm may only be a mall margin showing brown staining.
2.1 Single Layered Cells cont.

CINtec® PLUS positive: Single-layered cell with a brown cytoplasm and red nucleus. Mat.: ThinPrep, HSIL 40x

CINtec® PLUS positive: Several single-layered cells with a brown cytoplasm and red nucleus. Mat.: ThinPrep, HSIL 40x
Cells in Clusters
2.2 Cells in Clusters; Description

1. Exact interpretation has to be made

2. Confirm that nucleus and cytoplasm showing brown and red staining are in one plain, i.e. refer to one cell

3. Important to use the micrometer-screw

4. Typically a diffuse staining „pattern“, i.e. a continuous staining of (almost) all cells for p16 is seen in cases where cell clusters show double-immunoreactive cells

5. Exact differentiation between specific diffuse staining and unspecific mucus background has to be made
2.2 Cluster Examples

CINtec® PLUS positive: Cluster; cells with brown cytoplasm and red nucleus, diffuse p16 staining.
Mat.: ThinPrep, HSIL 20x
2.2 Cluster Examples

CINtec® PLUS positive: Cluster; cells with brown cytoplasm and red nucleus, diffuse p16 staining.
Mat.: ThinPrep, HSIL 40x
Staining Artefacts
2.3 Staining Artefacts Explanation

1. Background
   - Technical reasons: drying artefacts, fixation
   - Various intensities: weak / medium / strong
   - Various distribution: few cells to all cells
   - Homogeneous / heterogeneous

2. Bacteria
   - Biological reasons (unspecific IgG binding)
   - Stained brown or red

3. Edge effect
   - Technical reasons (mostly drying artefacts)

4. Goldstaub Phenomenon
   - Technical reasons
2.3 Background Examples

CINtec® PLUS negative: Background, Superficial and Intermediate cells.
Mat.: ThinPrep, WNL 10x
2.3 Background Examples

CINtec® PLUS negative: Background, Superficial and Intermediate cells.
Mat.: ThinPrep, WNL 10x

CINtec® PLUS negative: Background, Superficial cells and Mucus.
Mat.: ThinPrep, WNL  20x
2.3 Bacteria; Examples

CINtec® PLUS negative: Bacteria binding the HRP polymer, resulting in brown background stain.
Mat.: ThinPrep, WNL 40x
2.3 Bacteria; Examples

**CINtec® PLUS** negative: Bacteria binding the AP polymer, resulting in red background stain. 
Mat.: ThinPrep, WNL  20x

**CINtec® PLUS** negative: Bacteria binding the AP polymer, resulting in red background stain. 
Mat.: ThinPrep, WNL  40x
2.3 Goldstaub Phenomenon; Examples

CINtec® PLUS negative: Goldstaub Phenomenon.
Mat.: ThinPrep, WNL 10x

CINtec® PLUS negative: Goldstaub Phenomenon.
Mat.: ThinPrep, WNL 20x
Chapter 3
Staining Gallery
Cases Negative for CINtec® PLUS
3.1 Metaplasia

CINtec® PLUS negative: Metaplastic cells, some cells with p16 single staining.
Mat.: ThinPrep, WNL 20x

CINtec® PLUS negative: Metaplastic cells, some cells with p16 single staining.
Mat.: ThinPrep, WNL 40x
3.1 Metaplasia

CI\textsuperscript{N}tec\textsuperscript{\textregistered} PLUS negative: Metaplastic cells with p16 single staining.
Mat.: ThinPrep, WNL 40x
3.2 Endocervical Glandular Cells

CINtec® PLUS negative: Endocervical cells with cilia; p16 single stained.
Mat.: ThinPrep, WNL 40x

CINtec® PLUS negative: Endocervical cells with cilia; p16 single stained.
Mat.: ThinPrep, WNL 100x
3.2 Endocervical Glandular Cells

CINtec® PLUS negative: Endocervical cells, Ki-67 single stained. 
Mat.: ThinPrep, WNL 40x

CINtec® PLUS negative: Endocervical cells only p16 and only Ki-67 stained. 
Mat.: SurePath, WNL 40x
3.2 Endocervical Glandular Cells

CINtec® PLUS negative: Endocervical cells showing Ki-67 staining only. 
Mat.: ThinPrep, WNL 40x

CINtec® PLUS negative: Endocervical cell cluster with some cells that either stain Ki-67 only or p16 only, respectively. 
Mat.: ThinPrep, WNL 40x
3.2 Glandular Cells

CINtec® PLUS negative: Glandular cells, Ki-67 single stained.  
Mat.: ThinPrep, WNL 40x

CINtec® PLUS negative: Glandular cells, Ki-67 single stained.  
Mat.: ThinPrep, WNL 40x
3.3 Endometrium

CINtec® PLUS negative: Active endometrial cells; p16 single stained.
Mat.: ThinPrep, WNL 40x

CINtec® PLUS negative: Exodus; p16 single stained.
Mat.: ThinPrep, WNL 40x
3.3 Endometrium

CINtec® PLUS negative: Endometrial cells; p16 single stained.
Mat.: SurePath, WNL 10x

CINtec® PLUS negative: Endometrial cells; p16 single stained.
Mat.: SurePath, WNL 40x
3.3 Endometrium

CINtec® PLUS negative: Exodus; p16 single stained.
Mat.: ThinPrep, WNL 40x

CINtec® PLUS negative: Endometrial cells; p16 single stained.
Mat.: ThinPrep, WNL 40x
3.4 Atrophy

CINtec® PLUS negative: Atrophic cells; p16 single stained.
Mat.: ThinPrep, WNL 40x
3.4 Atrophy

CINtec® PLUS negative: Atrophic cell cluster with some atrophic cells; p16 single stained. Mat.: ThinPrep, WNL 20x

CINtec® PLUS negative: Atrophic cell cluster with some atrophic cells; p16 single stained. Mat.: ThinPrep, WNL 40x
3.5 Tissue Repair

CINtec® PLUS negative: Tissue Repair; p16 single stained.
Mat.: ThinPrep, WNL  20x

CINtec® PLUS negative: Tissue Repair; p16 single stained; Gardnarella-Infection.
Mat.: ThinPrep, WNL  40x
3.6 Mycosis & Bacteria

CINtec® PLUS negative: Mycosis without staining, Bacteria with brown colour.
Mat.: ThinPrep, WNL 40x
3.6 Leptothrix

CINtec® PLUS negative: Leptothrix without staining.
Mat.: SurePath, WNL 40x

CINtec® PLUS negative: Leptothrix without staining.
Mat.: SurePath, WNL 40x
3.6 Histiocytosis

CINtec® PLUS negative: Histiocytic giant cell; p16 single stained.
Mat.: ThinPrep, WNL 20x

CINtec® PLUS negative: Histiocytic giant cell; p16 single stained.
Mat.: SurePath, WNL 40x
3.6 Histiocytosis

CINtec® PLUS negative: Histiocytic giant cell with p16 and Ki-67 single stain only.
Mat.: SurePath, WNL 40x
3.6 Follicular Cervicitis

CINtec® PLUS negative: Follicular Cervicitis with Ki-67 single stained cells.
Mat.: Conventional smear, WNL 40x
3.7 LSIL

CINtec® PLUS negative: Koilocytosis; p16 single stained.
Mat.: ThinPrep, LSIL 40x

CINtec® PLUS negative: Koilocytosis; p16 single stained.
Mat.: ThinPrep, LSIL 100x
3.7 LSIL  Destaining Example

Papanicolaou staining
Mat.: Conventional smear, LSIL with Koilocyte 40x

CINtec® PLUS negative: Koilocyte without staining.
Mat.: Conventional smear, LSIL  40x
Chapter 4

Staining Gallery

Cases Positive for CINtec® PLUS
4.1 ASC-US / ASC-H

CINtec® PLUS positive: Cluster; cells with a brown cytoplasm and red nucleus.
Mat.: ThinPrep, ASC-H 40x

CINtec® PLUS positive: Cluster; cells with a brown cytoplasm and red nucleus.
Mat.: Thin Prep, ASC-H 40x
4.1 ASC-US / ASC-H

CINtec® PLUS positive: Cluster; cells with a brown cytoplasm and red nucleus. Mat.: ThinPrep, ASC-H 40x

CINtec® PLUS positive: Cells with a brown cytoplasm and red nucleus. Mat.: ThinPrep, ASC-H 40x
4.1 ASC-US / AGC

CINtec® PLUS positive: Glandular cluster; cells with a brown cytoplasm and red nucleus. Mat.: ThinPrep, AGC 20x

CINtec® PLUS positive: Glandular cluster; cells with a brown cytoplasm and red nucleus. Mat.: ThinPrep, AGC 40x
4.1 ASC-US / AGC

CINtec® PLUS positive: Glandular cluster; cells with a brown cytoplasm and red nucleus, one single-layered cell with brown cytoplasm and red nucleus.
Mat.: ThinPrep, AGC  40x
4.2 LSIL

CINtec® PLUS positive: Single-layered cell with a brown cytoplasm and red nucleus.
Mat.: ThinPrep, LSIL  20x

CINtec® PLUS positive: Single-layered cell with a brown cytoplasm and red nucleus.
Mat.: ThinPrep, LSIL  40x
4.2 LSIL

CINtec® PLUS positive: Cells with a brown cytoplasm and red nucleus.
Mat.: ThinPrep, LSIL 20x

CINtec® PLUS positive: Cells with a brown cytoplasm and red nucleus.
Mat.: ThinPrep, LSIL 40x
4.2 LSIL

CINtec® PLUS positive: Cells with a brown cytoplasm and red nucleus.
Mat.: ThinPrep, LSIL with Koilocytosis 20x

CINtec® PLUS positive: Cells with a brown cytoplasm and red nucleus.
Mat.: ThinPrep, LSIL with Koilocytosis 40x
4.2 LSIL

CINtec® PLUS positive: Two single-layered cells with a brown cytoplasm and red nucleus.
Mat.: ThinPrep, LSIL 20x
4.3 HSIL

CINtec® PLUS positive: Several cells with a brown cytoplasm and red nucleus.
Mat.: ThinPrep, HSIL  40x
4.3 HSIL

CINtec® PLUS positive: Cluster; cells with a brown cytoplasm and red nucleus.
Mat.: ThinPrep, HSIL 100x

CINtec® PLUS positive: Single-layered cells with a brown cytoplasm and red nucleus.
Mat.: ThinPrep, HSIL 100x
4.3 HSIL

**CINtec® PLUS** positive: Single-layered cells with a brown cytoplasm and red nucleus.
Mat.: SurePath, HSIL 100x

**CINtec® PLUS** positive: Single-layered cells with a brown cytoplasm and red nucleus.
Mat.: SurePath, HSIL 100x
4.3 HSIL

CINtec® PLUS positive: Cells with a brown cytoplasm and red nucleus.
Mat.: ThinPrep, HSIL 20x

CINtec® PLUS positive: Cells with a brown cytoplasm and red nucleus.
Mat.: ThinPrep, HSIL 40x
4.3 HSIL

CINtec® PLUS positive: Cells with a brown cytoplasm and red nucleus.
Mat.: ThinPrep, HSIL 100x

CINtec® PLUS positive: Cells with a brown cytoplasm and red nucleus.
Mat.: ThinPrep, HSIL 40x
4.4 Glandular Lesions

CINtec® PLUS positive: Cluster; cells with a brown cytoplasm and red nucleus.  
Mat.: ThinPrep, AGUS 100x

CINtec® PLUS positive: Glandular cluster; cells with a brown cytoplasm and red nucleus.  
Mat.: ThinPrep, AGUS 100x
Chapter 5
Staining Gallery
Examples for CINtec® PLUS Stain in Clusters
5.1 Cluster CINtec® PLUS Positive

CINtec® PLUS positive: Cluster; cells with a brown cytoplasm and red nucleus, diffuse p16 staining.
Mat.: ThinPrep, HSIL 20x

CINtec® PLUS positive: Cluster; cells with a brown cytoplasm and red nucleus, diffuse p16 staining.
Mat.: ThinPrep, HSIL 40x
5.1 Cluster CINtec® PLUS Positive

CINtec® PLUS positive: Cluster; cells with a brown cytoplasm and red nucleus, diffuse p16 staining.
Mat.: ThinPrep, HSIL  40x

CINtec® PLUS positive: Cluster; cells with a brown cytoplasm and red nucleus, diffuse p16 staining.
Mat.: ThinPrep, HSIL  20x
5.1 Cluster CINtec® PLUS Positive

CINtec® PLUS positive: Cluster; cells with a brown cytoplasm and red nucleus, diffuse p16 staining.
Mat.: ThinPrep, HSIL 20x

CINtec® PLUS positive: Cluster; cells with a brown cytoplasm and red nucleus, diffuse p16 staining.
Mat.: ThinPrep, HSIL 40x
5.1 Cluster CINtec® PLUS Positive

CINtec® PLUS positive: Cluster; cells with a brown cytoplasm and red nucleus.
Mat.: ThinPrep, HSIL 20x

CINtec® PLUS positive: Cluster; cells with a brown cytoplasm and red nucleus.
Mat.: ThinPrep, HSIL 40x
5.2 Cluster CINtec® PLUS Negative

CINtec® PLUS negative: Cluster with no dual-stained single cells, some cells with either p16 single stain or Ki-67 single stain, only; overlying nuclei.
Mat.: ThinPrep, WNL 20x
5.2 Cluster CINtec® PLUS
Negative

CINtec® PLUS negative: Cluster with no dual-stained cells, some cells with either p16 single stain or Ki-67 single stain
Mat.: ThinPrep, WNL  20x

CINtec® PLUS negative: Cluster with no dual-stained cells, some cells with either p16 single stain or Ki-67 single stain
Mat.: ThinPrep, WNL  40x
5.2 Cluster CINtec® PLUS Negative

CINtec® PLUS negative: Cluster with no dual-stained cells, some cells with either p16 single stain or Ki-67 single stain, only; overlying nuclei.
Mat.: ThinPrep, WNL 40x
Chapter 6

Staining Compendium
6.1 Conventionals

CINtec® PLUS positive: Single-layered cell with brown cytoplasm and red nucleus.
Mat.: HSIL 40x

CINtec® PLUS positive: Single-layered cell with brown cytoplasm and red nucleus.
Mat.: HSIL 100x

CINtec® PLUS positive: Several single-layered cells with a brown cytoplasm and red nucleus.
Mat.: HSIL 40x

CINtec® PLUS positive: Cells with a brown cytoplasm and red nucleus.
Mat.: HSIL 100x
6.1 Conventionals
Destaining Examples

Papanicolaou staining 20x
CINtec® PLUS negative: Metaplastic cells; p16 single stained only.
Mat.: WNL 20x

Papanicolaou staining 20x
CINtec® PLUS negative: Endocervical cells; some cells showing p16 single stain only.
Mat.: WNL 20x
6.1 Conventionals
Destaining Examples

Papanicolaou staining 40x

CINtec® PLUS positive: Single-layered cell with a brown cytoplasm and red nucleus.
Mat.: HSIL 40x

Papanicoloau staining 40x

CINtec® PLUS positive: Several single-layered cells with a brown cytoplasm and red nucleus.
Mat.: HSIL 40x
6.1 Conventionals
Destaining Examples

Papanicolaou staining 40x

CINtec® PLUS positive: Several single-layered cells with a brown cytoplasm and red nucleus. Mat.: HSIL 40x

Papanicolaou staining 40x

CINtec® PLUS positive: Cluster; cells with a brown cytoplasm and red nucleus. Mat.: HSIL 40x
6.1 Conventionals
Destaining Examples

Papanicolaou staining 40x

CINtec® PLUS positive: Cluster; cells with a brown cytoplasm and red nucleus.
Mat.: HSIL  40x

Papanicolaou staining 40x

CINtec® PLUS positive: Several cells with a brown cytoplasm and red nucleus.
Mat.: HSIL  40x
6.1 Conventionals
Destaining Examples

Papanicolaou staining 40x

CINtec® PLUS positive: Several single-layered cells with a brown cytoplasm and red nucleus.
Mat.: HSIL  40x

Papanicolaou staining 40x

CINtec® PLUS positive: Several single-layered cells with a brown cytoplasm and red nucleus.
Mat.: HSIL  40x
6.2 ThinPrep®

CINtec® PLUS positive: 3 single-layered cells, one with a brown cytoplasm and red nucleus. Mat.: HSIL  100x

CINtec® PLUS positive: Single-layered cell with a brown cytoplasm and red nucleus. Mat.: HSIL  100x

CINtec® PLUS positive: Cells with a brown cytoplasm and red nucleus. Mat.: HSIL  100x

CINtec® PLUS positive: 3 single-layered cells, one with a brown cytoplasm and red nucleus. Mat.: HSIL  100x
6.3 SurePath®

CINtec® PLUS positive: Several cells with a brown cytoplasm and red nucleus. 
Mat.: HSIL  100x

CINtec® PLUS positive: Cells with a brown cytoplasm and red nucleus. 
Mat.: HSIL  100x

CINtec® PLUS positive: Several cells with a brown cytoplasm and red nucleus. 
Mat.: HSIL  40x

CINtec® PLUS positive: Cells with a brown cytoplasm and red nucleus. 
Mat.: HSIL  100x