Help protect women from cervical cancer and from overtreatment

With the goal of bringing greater clarity to the continuum of patient management, Roche helps put the right information in your hands with solutions that address the unmet need in cervical cancer screening.

Identify women who can safely return to routine screening, those who need additional testing and those who need immediate management

- Stratifies women according to risk, based on pooled hrHPV and HPV 16/18 genotyping results
- Helps identify women with transforming lesions (p16/Ki-67 positive) who need colposcopy

For each woman, there’s a strategy
The Roche Cervical Cancer Screening Portfolio helps protect her from cancer and from overtreatment

Identify HPV positive women who require immediate management
Helps identify women with transforming lesions

Increase diagnostic accuracy for high-grade disease
Helps confirm the presence or absence of aCIN2 lesions in biopsies

REFERENCES:
6. Papanicolaou cytology: results from the European equivocal or mildly abnormal Papanicolaou cytology study.
Today’s screening strategies must balance maximizing benefits with minimizing potential harm for all women

Achieving the goals of cervical cancer screening has remained elusive

- Identifying as many women as possible at risk of precancer
- Avoiding unnecessary interventions for HPV positive women by sorting them into two groups:
  - Those at greatest risk for having high-grade disease now or developing it in the future
  - Those at lower risk and having HPV infections that are likely to resolve on their own

Current screening strategies are not enough

- Cytology has high specificity but low sensitivity, resulting in missed disease in women
- Up to 1/3 of cervical cancers occur in screened women with normal Pap cytology
- Pooled hrHPV testing has high sensitivity but low specificity, resulting in over-referral of healthy women who may not need colposcopy
  - These false-positives have an unnecessary adverse psychosocial impact on women, and may result in unnecessary interventions that place a large financial burden on the healthcare system

Addressing the conflicting challenges requires the right triage strategy

- First, use a test with high sensitivity and negative predictive value (NPV) to determine which women can safely return to routine screening
- Second, use tests that have high specificity and positive predictive value (PPV) to determine which women need further evaluation now and which women can be managed over time

The comprehensive strategy for diagnostic screening

With a portfolio of screening, triage and precancer diagnostic tests, Roche helps enable better patient outcomes by identifying women who can return safely to routine screening, reducing the number of colposcopies per CIN3 cases detected, as well as identifying more disease than current strategies.

The clinical dilemma with HPV positive women is to determine who would benefit most from colposcopy and who may be spared intervention.

Which strategy is right for her?
Roche brings clarity to screening, diagnosis and management

1. Identify women who can safely return to routine screening, those who need additional testing and those who need immediate management
   - Stratifies women according to risk, based on pooled hrHPV and HPV 16/18 genotyping results

2. Identify HPV positive women who require immediate management
   - Helps identify women with transforming lesions (p16/Ki-67 positive) who need colposcopy

3. Increase diagnostic accuracy for high-grade disease
   - Helps diagnose and confirm the presence or absence of aCIN2 lesions (p16 positive) in biopsies obtained during colposcopies
Testing for HPV 16 and HPV 18 brings clarity
Identify women at greatest risk

The cobas® HPV Test is the only clinically validated, CE-marked and FDA-approved* test that simultaneously provides pooled results on known “high-risk” genotypes and individual results on the 2 highest-risk genotypes, HPV 16 and HPV 18, giving 3 results in just 1 test.

The cobas® HPV Test adds greater specificity to screening strategies than pooled hrHPV alone
• In a 10-year study of women with normal cytology, women HPV 16 positive or HPV 18 positive were more likely to have ≥CIN3 than women who were positive for other pooled HPV genotypes.
• Women HPV 16 positive and/or HPV 18 positive are at increased risk of ≥CIN3 even if they have normal baseline and repeat cytologies.\(^1\)

Primary screening with the cobas® HPV Test
(Not approved in the US or Canada)
• When used in primary screening, HPV with 16/18 genotyping was more efficient than the current standard of care, significantly reducing the number of colposcopies necessary per ≥CIN3 detected.\(^3\)

The optimal primary screening strategy focuses medical attention on women with genotypes HPV 16 or 18, and triages other high-risk HPV genotypes.\(^4\)

HPV DNA-based screening reduces the incidence of cervical cancer within 4 to 5 years compared to cytology-based screens.\(^16\)

Uncover disease that is missed by cytology alone
• In the ATHENA study, the cobas® HPV Test found 92% of cases of ≥CIN3 in the overall population compared to 53% found by cytology.\(^2\)
• Nearly 1 in 7 women with normal cytology (NILM) who were HPV 16 positive actually had high-grade cervical disease that was missed by cytology.\(^4\)

The cobas® HPV Test helps protect women from overtreatment
• The cobas® HPV Test identifies all high-risk HPV genotypes as well as individual results for the most aggressive HPV genotypes 16 & 18:\(^6\)
  - Protects healthy women from unnecessary intervention, allowing them to return to routine screening if results are negative
  - Identifies women who need immediate intervention if HPV 16/18 positive

The landmark ATHENA study provided clinical evidence to support the US guidelines in recognizing the benefits of identifying HPV 16 or HPV 16/18.\(^13\)

<table>
<thead>
<tr>
<th></th>
<th>Cobas® HPV Test positive result</th>
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<tbody>
<tr>
<td>NILM</td>
<td>14 pooled Cobas® HPV Test result</td>
</tr>
<tr>
<td>hpHPV+</td>
<td>12 hrHPV+</td>
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<tr>
<td>hpHPV+</td>
<td>hpHPV+</td>
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Absolute risk of ≥CIN2 stratified by hrHPV status in the ATHENA NILM population*1

<table>
<thead>
<tr>
<th>hpHPV−</th>
<th>hrHPV−</th>
<th>hrHPV+</th>
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</thead>
<tbody>
<tr>
<td>NLM</td>
<td>1.2</td>
<td>0.8</td>
</tr>
<tr>
<td>12 hrHPV+</td>
<td>4.6</td>
<td>7.0</td>
</tr>
<tr>
<td>14 pooled Cobas® HPV Test result</td>
<td>13.6</td>
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Absolute risk measurement estimates are estimates based on raw study data.

The patients described in this brochure are not actual patients, but rather are representative of patient scenarios often seen in clinical practice.

ATHENA = Addressing THE Need for Advanced HPV Diagnosis; CE-marked = verification that products meet European Union safety, health, or environmental requirements; FDA = US Food and Drug Administration; NILM = negative for intraepithelial lesion or malignancy.
In cervical cancer screening

**CINtec® PLUS, an advanced biomarker combination**

The CINtec® PLUS immunocytochemistry assay is for the simultaneous qualitative detection of the p16INK4a and Ki-67 proteins in cervical cytology preparations.

- Identifies underlying high-grade cervical disease
- Helps identify women with transforming lesions (p16/Ki-67 positive) who need colposcopy

**Identify HPV positive women requiring immediate management**

- Demonstrates high sensitivity (>90%) for the detection of established high-grade disease in Pap negative, HPV positive women ≥30y
- Provides high specificity, enabling triage of 75% of women back to routine testing
- May reduce the number of unnecessary colposcopies by up to 50%

**Challenges with diagnostic accuracy exist**

- It is important to distinguish between high-grade CIN and its morphologic mimics to avoid overtreatment of false-positive cases and undertreatment of false-negative cases
- Histological assessment of cervical dysplasia is complicated by interobserver variability
- Lesions may be missed due to small representation or severe inflammation

**Significantly increased diagnostic accuracy with the CINtec® p16 Histology product**

- 13% increase for detecting ≥CIN2 without a loss in specificity
- 45% reduction in false-negative interpretations
- 30% overall increase in interobserver agreement for diagnosing ≥CIN2

**Identify more occult lesions**

- 22% increase in identification of CIN lesions from H&E biopsies initially diagnosed as negative

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In cervical biopsy diagnosis

**CINtec® p16 Histology sets a new standard for diagnostic excellence**

The CINtec® p16 Histology product is an immunohistochemistry assay for the qualitative detection of the p16INK4a protein on slides prepared from formalin-fixed, paraffin-embedded cervical biopsies.

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In cervical cancer screening

**CINtec® PLUS provides high sensitivity and high specificity in a single test**

- Provides an option for immediate management of women testing Pap negative/HPV positive especially when HPV 16/18 results are negative or unknown
- The first tool for efficient management of women with LSLL cytology

**A positive test result with CINtec® PLUS is an indicator for women to be referred for colposcopy**

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<table>
<thead>
<tr>
<th>The Wolfsburg Study</th>
<th>(n=425 women tested Pap negative but hrHPV positive)</th>
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<tbody>
<tr>
<td>Sensitivity in Pap Negative/hrHPV Positive Women ≥30y</td>
<td></td>
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<tr>
<td>CINtec® PLUS</td>
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<tr>
<td>≥CIN2</td>
<td>92%</td>
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<tr>
<td>≥CIN3</td>
<td>96%</td>
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<th>Biopsy-confirmed cases</th>
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<tr>
<td>≥CIN2 (n=127), ≥CIN3 (n=26)</td>
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**Rates of Positivity in Pap Negative/hrHPV Positive Women ≥30y**

| CINtec® PLUS | | |
|--------------|-----------------|
| Negative cases | 25% |
| Positive cases | 79% |

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<thead>
<tr>
<th>CINtec® PLUS in LSIL Cytology: Data from EEMAPS®</th>
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<tr>
<td>(n=137 biopsy-confirmed cases of ≥CIN2)</td>
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<tr>
<td>Sensitivity</td>
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<td>Specificity</td>
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<td>Colposcopy referrals</td>
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<tr>
<td>CINtec® PLUS</td>
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<td>Pooled hrHPV</td>
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| EEMAPS = European Equivocal or Mildly Abnormal Pap Cytology Study; LSLL = Low-grade squamous intraepithelial lesion. | H&E = Hematoxylin and eosin [stain]. |