PUBLICATION SUMMARY

Genotype-Specific HPV E6/E7 mRNA Triage Improves CIN2+ Detection Efficiency Compared to Cytology

HPV mRNA triage using the Mel-Mont Medical Mia™ Comprehensive Cervical Cancer Test shifts cervical cancer screening from detection of viral presence to identification of biologically active disease, resulting in fewer false positives, fewer invasive follow up procedures, and more cost-effective treatment.

Introduction

Cervical cancer screening has transitioned toward primary HPV DNA testing due to its superior sensitivity; however, its reduced specificity leads to a substantial number of unnecessary colposcopy referrals. Cytology remains the standard triage method but is limited by subjectivity and variability. There is a clear clinical need for more precise, objective triage tools that better distinguish transient HPV infections from those with true oncogenic potential.
This study evaluates the clinical performance of the proprietary Mel-Mont Medical genotype-specific 7-type HPV E6/E7 mRNA test as a triage method for HPV DNA–positive women within a population-based screening program.

Key Insights

- **Maintains Sensitivity While Improving Precision**
  The 7-type HPV mRNA test delivers comparable sensitivity to cytology (~71% vs 72%) while significantly improving specificity (+19 percentage points) and positive predictive value (+47%), enabling more accurate identification of clinically meaningful disease.

- **Substantially Reduces Unnecessary Procedures**
  mRNA triage reduces false positives by 34% and decreases colposcopies required per CIN2+ case from 5.2 to 3.6 (31% reduction), demonstrating meaningful improvements in clinical efficiency and patient burden.

- **Superior Risk Stratification Through Transcriptional Activity**
  Detection of E6/E7 mRNA differentiates active oncogenic infections vs transient HPV presence, with CIN2+ risk of 28.1% in mRNA-positive vs 5.9% in mRNA-negative patients, providing clear clinical separation of high- and low-risk populations.

- **Genotype-Specific Insights Enhance Clinical Decision-Making**
  The test enables granular, genotype-level risk stratification, with highest PPVs observed in:
  - HPV16: 47.7%
  - HPV33: 39.2%
  - HPV31: 32.2%

  This exceeds DNA-based risk estimates and supports more targeted management.

- **Improves Screening Efficiency Without Compromising Safety**

  High negative predictive value (~94.6%) supports safe management of mRNA-negative patients within standard surveillance intervals while focusing interventions on those at highest risk.

- **Enables a Shift to Precision, Molecular-Based Screening**
  By replacing subjective cytology with objective molecular detection of oncogenic activity, HPV mRNA triage supports scalable, standardized, and potentially self-sample-compatible screening models.

Study Design & Population

This population-based cohort study was conducted within the Norwegian Cervical Cancer Screening Programme between 2019 and 2023, with follow-up through October 2024. A total of 34,721 women aged 25–69 underwent primary HPV DNA screening using the Cobas 4800 assay.

Among these, 1,896 HPV DNA–positive women were included in the triage cohort. Each participant underwent parallel triage using:

- Liquid-based cytology (≥ASC-US considered positive)
- Genotype-specific 7-type HPV E6/E7 mRNA testing targeting HPV types 16, 18, 31, 33, 45, 52, and 58

The primary endpoint was histologically confirmed cervical intraepithelial neoplasia grade 2 or worse (CIN2+).

Performance Results

1. Triage Positivity and Referral Impact
The HPV mRNA test demonstrated a substantially lower positivity rate compared to cytology (33.4% vs. 50.3%), representing a 34% relative reduction in false positive results. This translated into a meaningful decrease in unnecessary follow up procedures, with the mRNA-based approach requiring 3.6 colposcopies per CIN2+ case detected versus 5.2 using cytology: a 31% reduction in procedures.

2. Diagnostic Performance
The HPV mRNA test maintained sensitivity comparable to cytology while significantly improving specificity and positive predictive value:

- Sensitivity: 70.6% (mRNA) vs. 72.2% (cytology)
- Specificity: 72.3% vs. 53.0%
- Positive Predictive Value (PPV): 28.1% vs. 19.1%
- Negative Predictive Value (NPV): 94.6% vs. 93.0%

These findings demonstrate that mRNA triage preserves detection of clinically significant disease while reducing false positives and unnecessary interventions.

3. Risk Stratification
HPV mRNA testing provided superior risk discrimination compared to cytology. Among HPV DNA–positive women:

- CIN2+ prevalence was 28.1% in mRNA-positive cases
- CIN2+ prevalence was 5.9% in mRNA-negative cases

This marked separation between high- and low-risk groups highlights the clinical utility of detecting transcriptionally active infections.

4. Genotype-Specific Insights
The genotype-specific nature of the test enabled refined risk stratification:
- HPV16 mRNA: 47.7% PPV
- HPV33 mRNA: 39.2%
- HPV31 mRNA: 32.2%

Within HPV16 DNA–positive women, mRNA testing further stratified risk:

- 47.7% CIN2+ when mRNA-positive
- 9.7% when mRNA-negative

This demonstrates the added clinical value of assessing oncogenic activity beyond HPV presence alone.

5. Clinical Implications

The findings support several key clinical advantages of genotype-specific HPV mRNA triage:

I. Reduction in Unnecessary Procedures
Significant decreases in test positivity and colposcopy referrals improve the benefit–harm balance of screening programs.

II. Improved Diagnostic Precision
Higher specificity and PPV enable more accurate identification of women at true risk of high-grade disease.

III. Objective, Molecular-Based Triage
Eliminates reliance on subjective cytology interpretation and associated variability.

IV. Compatibility with Self-Sampling
Enables broader access and scalability, particularly in decentralized or resource-limited settings.

Conclusion

Genotype-specific HPV E6/E7 mRNA testing represents a clinically effective and operationally scalable triage strategy for HPV DNA positive women. By maintaining sensitivity while significantly improving specificity and predictive accuracy, this approach enables more precise identification of clinically meaningful disease and reduces unnecessary follow up procedures.

These results support the integration of mRNA-based triage tests such as the Mia Comprehensive Cervical Cancer Test into cervical cancer screening programs as a key component of a precision, risk-adapted screening paradigm.