SOX1/PAX1 Methylation Testing for Triage of Cervical Type 3 Transformation Zone (TZ3)

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Background

- Cervical cancer is the fourth most common female malignancy globally; hrHPV infection is the main cause.
- **TZ3**: Squamous-columnar junction retracts into the cervical canal, leading to **high underdiagnosis rate (22.4%)** in colposcopy and biopsy.
- Traditional screening (HPV genotyping and cytology test) has low specificity, poor triage efficiency, and unstable performance in TZ3.
- **SOX1/PAX1 methylation** is a promising epigenetic biomarker for cervical precancerous lesions.

Methods

- Study design: Cross-sectional study
- Population: 259 women with **colposcopically confirmed TZ3**
- Tests: HPV genotyping, Cytology test, SOX1/PAX1 methylation (qMSP)
- Gold standard: Histopathology (CIN2+ as endpoint)
- Outcomes: Sensitivity, specificity, PPV, NPV, AUC, the number needed to colposcopy(NNC), risk stratification

Objective

To evaluate the **diagnostic efficacy, triage value, and risk stratification performance** of SOX1/PAX1 methylation testing in women with TZ3, especially postmenopausal subgroup.

Diagnostic strategy	Sensitivity(%) (n/N)95%CI	Speciticity(%) (n/N)95%CI	PPV(%) (n/N)95%CI	NPV(%) (n/N)95%CI	Compared with HPV 16/18	
					Relative Sensitivity (95%CI)	Relative Sensitivity (95%CI)
HPV16/18	29.41(10/34) 16.83-46.17	79.56(179/225) 73.81-84.31	17.86(10/56) 10.00-29.84	88.18(179/203) 83.01-91.93	1	1
hr_HPV	85.29(29/34) 69.87-93.55	15.11(34/225) 11.02-20.37	13.18(29/220) 9.34-18.29	87.18(34/39) 73.29-94.40	2.90 1.69-4.97	0.19 0.14-0.26
TCT(≥ASCUS)	76.47(26/34) 60.00-87.56	55.56(125/225) 49.02-61.90	20.63(26/126) 14.49-28.52	93.98(125/133) 88.58-96.92	2.60 1.50-4.52	0.70 0.61-0.80
Methylation	91.18(31/34) 77.04-96.95	84.00(189/225) 78.65–88.21	46.27(31/67) 34.86–58.08	98.44(189/192) 95.51–99.47	3.10 1.82-5.27	1.06 0.97-1.15

Table Diagnostic performance of different diagnostic strategies for CIN2+ in the women with TZ3 under colposcopy

Low-risk HPV, including HPV genotypes types 6, 11, 42, 43, 44 and CP8304; high-risk HPV, including HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66 and 68; Abbreviations: SD, standard deviation.; NILM, negative for intraepithelial lesion or malignancy; AS-CUS, atypical squamous cells of underdetermined significance or worse; LSIL+, low-grade squamous intraepithelial lesion or worse; HSIL+, high-grade squamous intraepithelial lesion or worse.

Results

1.Diagnostic Performance for CIN2+

- **Methylation**: Sensitivity 91.18%, Specificity 84.00%, AUC 0.876, NPV 98.44%
- Significantly outperforms hrHPV, TCT, and HPV16/18 genotyping

2.Triage Efficiency (In hrHPV+ TZ3 women)

- NNC (Number Needed for Colposcopy): Methylation = 2.19
- HPV16/18 = 5.60; TCT = 4.48

3.Risk Stratification

Methylation (+): CIN2+ risk = 46.27%

Methylation (+): Residual CIN2+ risk = 1.56% (≈30-fold difference)

4.**Postmenopausal TZ3 Subgroup (n=118)**

- Methylation: Sensitivity 83.33%, Specificity 84.16%, NPV 97.70%
- Stable and reliable performance in this high- risk subgroup

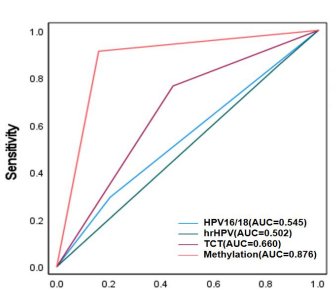

Figure ROC of different methods for TZ3 patients with CIN2+. AUC: area under the curve

Conclusions

- SOX1/PAX1 methylation shows **superior diagnostic accuracy** for CIN2+ in TZ3 women.
- It achieves **optimal triage efficiency** and reduces unnecessary colposcopies.
- It enables **precise risk stratification** and reliable “safe exclusion”.
- It performs stably in postmenopausal TZ3 women and solves clinical pain points of traditional methods.