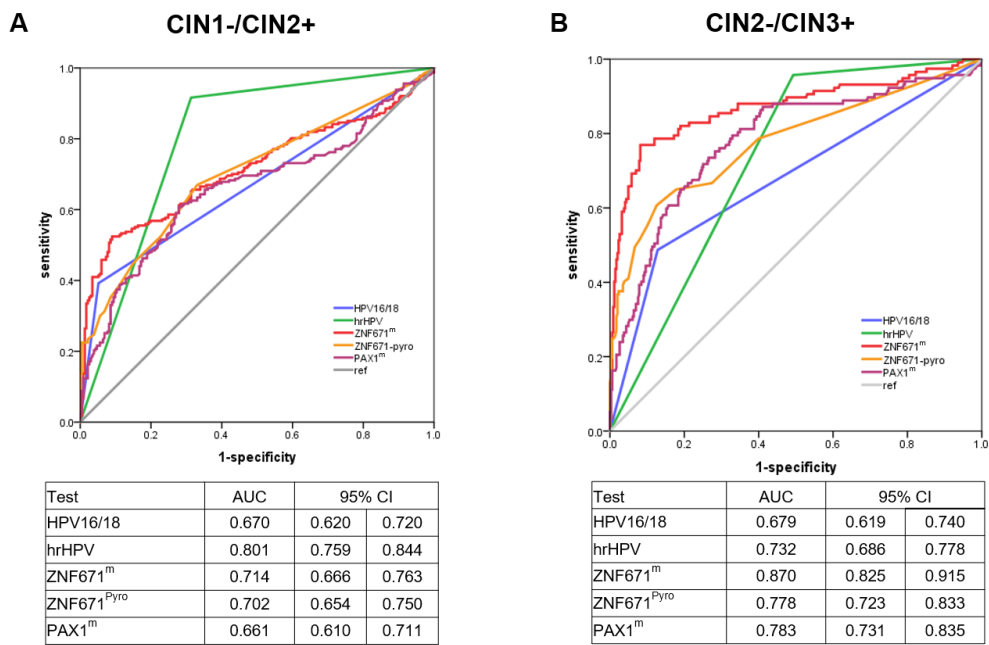


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**Supplemental information**

**ZNF671 methylation test in cervical scrapings  
for cervical intraepithelial neoplasia grade 3  
and cervical cancer detection**

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**Figure S1** Receiver operating characteristic (ROC) curves for the performance of HPV16/18, hrHPV, the methylation status of ZNF671 gene by qMSP (ZNF671<sup>m</sup>), of ZNF671 gene by pyrosequencing (ZNF671<sup>Pyro</sup>) and of PAX1 gene by qMSP (PAX1<sup>m</sup>) to distinguish different diagnosis groups in training set. (A) CIN1-/CIN2+; (B) CIN2-/CIN3+. Related to Table 2.

**Table S1 Performance of molecular triage for the detection of CIN2+ among 281 hrHPV-positive women (training set)**

| Molecular triage algorithms                          | Colposcopy referral rates(%)<br>(n/N) | Sensitivity<br>(%)(n/N)95% CI | Specificity<br>(%)(n/N)95% CI | PPV(%)<br>(n/N)95% CI          | NPV(%)<br>(n/N)95% CI        | NNC  | Compared to HPV16/18             |                                  | Compared to HPV16/18 or PAX1 <sup>m</sup> |                                  |
|--|---------------------------------------|-------------------------------|-------------------------------|--------------------------------|------------------------------|------|----------------------------------|----------------------------------|---|----------------------------------|
|  |                                       |                               |                               |                                |                              |      | Relative Sensitivity<br>(95% CI) | Relative specificity<br>(95% CI) | Relative Sensitivity<br>(95% CI)          | Relative specificity<br>(95% CI) |
|  |                                       |                               |                               |                                |                              |      | HPV16/18                         | 35.94(101/281)                   | 42.79(89/208)<br>36.25-49.82              | 83.56(61/73)<br>72.65-90.86      |
| PAX1 <sup>m</sup>                                    | 49.47(139/281)                        | 54.81(114/208)<br>47.78-61.66 | 65.75(48/73)<br>53.63-76.21   | 82.01(114/139)<br>74.40-87.81  | 33.80(48/142)<br>26.22-42.28 | 1.22 | 1.28<br>(1.06-1.55)              | 0.79<br>(0.64-0.96)              | -   | -                                |
| ZNF671 <sup>m</sup>                                  | 43.77(123/281)                        | 52.88(110/208)<br>45.87-59.79 | 82.19(60/73)<br>60.90-73.28   | 89.43(110/123)<br>82.28-94.03  | 37.97(60/158)<br>30.48-46.06 | 1.12 | 1.24<br>(1.02-1.50)              | 0.98<br>(0.85-1.13)              | -   | -                                |
| HPV16/18 or PAX1 <sup>m</sup>                        | 65.12(183/281)                        | 71.63(149/208)<br>64.91-77.55 | 53.42(39/73)<br>41.44-65.05   | 81.42(149/183)<br>74.86-86.63  | 39.80(39/98)<br>30.20-50.21  | 1.23 | 1.67<br>(1.47-1.91)              | 0.64<br>(0.53-0.77)              | 1 (ref)                                   | 1 (ref)                          |
| HPV16/18 or ZNF671 <sup>m</sup>                      | 59.79(168/281)                        | 70.19(146/208)<br>63.41-76.22 | 69.86(51/73)<br>57.85-79.76   | 86.90(146/168)<br>80.63-91.43  | 45.13(51/113)<br>35.85-54.75 | 1.15 | 1.64<br>(1.44-1.87)              | 0.84<br>(0.75-0.93)              | 0.98<br>(0.91-1.06)                       | 1.31<br>(1.11-1.58)              |
| ZNF671 <sup>m</sup> or PAX1 <sup>m</sup>             | 58.36(164/281)                        | 63.94(133/208)<br>56.97-70.39 | 57.53(42/73)<br>45.43-68.84   | 81.10(133/164)<br>474.09-86.61 | 35.90(42/117)<br>27.39-45.35 | 1.23 | 1.49<br>(1.24-1.80)              | 0.69<br>(0.55-0.87)              | 0.89<br>(0.81-0.98)                       | 1.08<br>(0.90-1.28)              |
| HPV16/18 or ZNF671 <sup>m</sup> or PAX1 <sup>m</sup> | 71.89(202/281)                        | 78.37(163/208)<br>82.02-83.63 | 46.58(34/73)<br>34.95-58.86   | 80.69(163/202)<br>74.43-85.76  | 43.04(34/79)<br>32.11-54.65  | 1.24 | 1.83<br>(1.59-2.11)              | 0.56<br>(0.45-0.70)              | 1.09<br>(1.04-1.15)                       | 0.87<br>(0.77-0.98)              |

<sup>m</sup>: methylation; PPV: positive predictive values; NPV: positive predictive values; NNC: the number of colposcopies needed to detect per CIN2+ cases. Related to Table 2.

**Table S2 Performance of triage for the detection of CIN2+ among 391 hrHPV-positive women (validation set)**

| Triage algorithms                              | Colposcopy referral rates(%)<br>(n/N) | Sensitivity (%)<br>(n/N)95% CI | Specificity (%)<br>(n/N)95% CI | PPV(%)<br>(n/N)95% CI         | NPV(%)<br>(n/N)95% CI        | NNC  | Compared to TCT(ASCUS+)          |                                  | Compared to HPV16/18 or TCT(ASCUS+) |                                  |
|--|---------------------------------------|--------------------------------|--------------------------------|-------------------------------|------------------------------|------|----------------------------------|----------------------------------|-------------------------------------|----------------------------------|
|  |                                       |                                |                                |                               |                              |      | Relative Sensitivity<br>(95% CI) | Relative specificity<br>(95% CI) | Relative Sensitivity<br>(95% CI)    | Relative specificity<br>(95% CI) |
| TCT(ASCUS+)                                    | 74.42(291/391)                        | 81.43(228/280)<br>76.27-85.71  | 43.24(48/111)<br>33.98-52.98   | 78.35(228/291)<br>73.08-82.85 | 48.00(48/100)<br>37.99-58.17 | 1.28 | 1 (ref)                          | 1 (ref)                          | -                                   | -                                |
| HPV16/18                                       | 41.94(164/391)                        | 48.21(135/280)<br>42.25-54.23  | 73.87(82/111)<br>64.52-81.54   | 82.32(135/164)<br>75.42-87.66 | 36.12(82/227)<br>29.94-42.78 | 1.21 | 0.59<br>(0.52-0.68)              | 1.71<br>(1.34-2.18)              | -                                   | -                                |
| ZNF671 <sup>m</sup>                            | 51.15(200/391)                        | 58.93(165/280)<br>52.90-64.70  | 68.47(76/111)<br>58.86-76.77   | 82.50(165/200)<br>76.36-87.36 | 39.79(76/191)<br>32.87-47.13 | 1.21 | 0.72<br>(0.65-0.80)              | 1.58<br>(1.26-1.99)              | -                                   | -                                |
| HPV16/18 or TCT(ASCUS+)                        | 85.17(333/391)                        | 91.43(256/280)<br>87.36-94.32  | 30.63(34/111)<br>22.42-40.20   | 76.88(256/333)<br>71.90-81.22 | 58.62 (34/58)<br>44.96-71.14 | 1.30 | 1.12<br>(1.07-1.18)              | 0.71<br>(0.59-0.85)              | 1 (ref)                             | 1 (ref)                          |
| HPV16/18 or ZNF671 <sup>m</sup>                | 67.26(263/391)                        | 74.29(208/280)<br>68.67-79.22  | 50.45(56/111)<br>40.86-60.01   | 79.09(208/263)<br>73.57-83.74 | 43.75(56/128)<br>35.09-52.79 | 1.26 | 0.91<br>(0.84-1.00)              | 1.17<br>(0.89-1.52)              | 0.81<br>(0.76-0.87)                 | 1.65<br>(1.26-2.16)              |
| ZNF671 <sup>m</sup> or TCT(ASCUS+)             | 82.10(321/391)                        | 88.21(247/280)<br>83.71-91.64  | 33.33(37/111)<br>24.84-42.99   | 76.95(247/321)<br>71.87-81.36 | 52.86(37/70)<br>40.64-64.76  | 1.30 | 1.08<br>(1.04-1.13)              | 0.77<br>(0.66-0.90)              | 0.96<br>(0.93-1.00)                 | 1.09<br>(0.87-1.37)              |
| HPV16/18 or ZNF671 <sup>m</sup> or TCT(ASCUS+) | 89.26(349/391)                        | 94.64(265/280)<br>91.14-96.86  | 24.32(27/111)<br>16.90-33.56   | 75.93(265/349)<br>71.03-80.25 | 64.29(27/42)<br>47.99-78.00  | 1.32 | 1.16<br>(1.11-1.22)              | 0.56<br>(0.44-0.72)              | 1.04<br>(1.01-1.06)                 | 0.79<br>(0.67-0.94)              |

<sup>m</sup>: methylation; PPV: positive predictive values; NPV: positive predictive values; NNC: the number of colposcopies needed to detect per CIN2+ cases. Related to Table 3.

**Table S3 The cost of combination tests for detection of CIN3+ in 633 women (validation set)**

| Algorithms                                     | Total costs (\$) | The cost needed to detect per CIN3+ cases (\$) |
|--|------------------|--|
| HPV16/18 or TCT(ASCUS+)                        | 26682.52         | 163.70   |
| HPV16/18 or ZNF671 <sup>m</sup>                | 25110.94         | 159.94   |
| HPV16/18 or ZNF671 <sup>m</sup> or TCT(ASCUS+) | 35449.64         | 206.10   |

The total cost including gynecological examination cost, combination test cost (combined with hrHPV test), referral service cost, colposcopy cost and pathological examination cost. The cost data (per person) of gynecological examination (2.32\$), hrHPV test (10.85\$), TCT (10.23\$), referral service (1.55\$), colposcopy (9.30\$) and pathological examination (24.79\$) were collected from the published literature.<sup>34</sup> The cost of ZNF671<sup>m</sup> test were calculated according the data in our laboratory (11.62\$). Related to Table 5.