

## Supplementary Online Content

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**eTable 1.** Number of Discordant Pairs and McNemar Test for Discordant Pairs Between Different Triage Strategies Among Cases of Cervical Intraepithelial Neoplasia

**eTable 2.** Characteristics of Women With Negative or Normal Triage Test Results Women Stratified by Receipt of Disease Verification by Histopathological Examination to Adjust for Verification Bias

**eFigure.** STARD Diagram

This supplementary material has been provided by the authors to give readers additional information about their work.

**eTable 1.** Number of Discordant Pairs and McNemar Test for Discordant Pairs Between Different Triage Strategies Among Cases of Cervical Intraepithelial Neoplasia

| Test 1                                 | Test 2                                 | Total (n) | Test1/Test2 result |     |     |     | Crude            |                  | p-value McNemar <sub>a</sub> | McNemar mid-p test** |
|--|--|-----------|--------------------|-----|-----|-----|------------------|------------------|------------------------------|----------------------|
|  |  |           | -/-                | +/- | -/+ | +/+ | Sens (test1)     | Sens (test2)     |                              |                      |
| <b>CIN2+</b>                           |  |           |                    |     |     |     |                  |                  |                              |                      |
| HPV16                                  | LBC                                    | 125       | 23                 | 48  | 38  | 16  | 51.6 (42.5-60.6) | 42.9 (34.1-52.0) | .28                          | -                    |
| HPV18                                  | LBC                                    | 126       | 61                 | 11  | 52  | 2   | 10.2 (5.6-16.9)  | 42.9 (34.1-52.0) | <.001                        | -                    |
| HPV16/18                               | LBC                                    | 126       | 17                 | 55  | 36  | 18  | 58.3 (49.1-67.0) | 42.9 (34.1-52.0) | .046                         | -                    |
| HPV16+ → reflex LBC (ASCUS+) if HPV16- | LBC                                    | 125       | 23                 | 48  | 0   | 54  | 81.7 (73.9-88.1) | 42.9 (34.1-52.0) | <.001                        | <.001                |
| HPV16/18+ → reflex LBC if HPV 16/18 -  | LBC                                    | 126       | 17                 | 55  | 0   | 54  | 86.6 (79.4-92.0) | 42.9 (34.1-52.0) | <.001                        | <.001                |
| HPV16                                  | HPV16/18                               | 125       | 53                 | 0   | 8   | 64  | 51.6 (42.5-60.6) | 58.3 (49.1-67.0) | 0.008                        | .004                 |
| HPV16+ → reflex LBC (ASCUS+) if HPV16- | HPV16/18                               | 125       | 17                 | 36  | 6   | 66  | 81.7 (73.9-88.1) | 58.3 (49.1-67.0) | <.001                        | <.001                |
| HPV16/18+ → reflex LBC if HPV 16/18 -  | HPV16/18                               | 126       | 17                 | 36  | 0   | 73  | 86.6 (79.4-92.0) | 58.3 (49.1-67.0) | <.001                        | <.001                |
| HPV16/18+ → reflex LBC if HPV 16/18 -  | HPV16+ → reflex LBC (ASCUS+) if HPV16- | 125       | 17                 | 6   | 0   | 102 | 86.6 (79.4-92.0) | 81.7 (73.9-88.1) | .03                          | .02                  |
| <b>&lt;CIN2+</b>                       |  |           |                    |     |     |     |                  |                  |                              |                      |
| HPV16                                  | LBC                                    | 1020      | 462                | 292 | 231 | 35  | 67.8 (64.8-70.6) | 74.0 (71.2-76.6) | .008                         | -                    |
| HPV18                                  | LBC                                    | 1022      | 615                | 141 | 240 | 26  | 83.6 (81.2-85.8) | 74.0 (71.2-76.6) | <.001                        | -                    |
| HPV16/18                               | LBC                                    | 1022      | 349                | 407 | 209 | 57  | 54.4 (51.3-57.5) | 74.0 (71.2-76.6) | <.001                        | -                    |
| HPV16+ → reflex LBC (ASCUS+) if HPV16- | LBC                                    | 1020      | 462                | 292 | 0   | 266 | 45.1 (42.0-48.2) | 74.0 (71.2-76.6) | <.001                        | <.001                |

| Test 1                                 | Test 2                                 | Total (n) | Test1/Test2 result |       |       |       | Crude            |                  | p-value McNemar <sup>a</sup> | McNemar mid-p test <sup>**</sup> |
|--|--|-----------|--------------------|-------|-------|-------|------------------|------------------|------------------------------|----------------------------------|
|  |  |           | - / -              | + / - | - / + | + / + | Sens (test1)     | Sens (test2)     |                              |                                  |
| HPV16/18+ → reflex LBC if HPV 16/18 -  | LBC                                    | 1022      | 349                | 407   | 0     | 266   | 34.0 (31.1-37.0) | 74.0 (71.2-76.6) | <.001                        | <.001                            |
| HPV16                                  | HPV16/18                               | 1027      | 560                | 0     | 136   | 331   | 67.8 (64.8-70.6) | 54.4 (51.3-57.5) | <.001                        | <.001                            |
| HPV16+ → reflex LBC (ASCUS+) if HPV16- | HPV16/18                               | 1020      | 349                | 209   | 113   | 349   | 45.1 (42.0-48.2) | 54.4 (51.3-57.5) | <.001                        | -                                |
| HPV16/18+ → reflex LBC if HPV 16/18 -  | HPV16/18                               | 1022      | 349                | 209   | 0     | 464   | 34.0 (31.1-37.0) | 54.4 (51.3-57.5) | <.001                        | <.001                            |
| HPV16/18+ → reflex LBC if HPV 16/18 -  | HPV16+ → reflex LBC (ASCUS+) if HPV16- | 1020      | 349                | 113   | 0     | 558   | 34.0 (31.1-37.0) | 45.1 (42.0-48.2) | <.001                        | <.001                            |

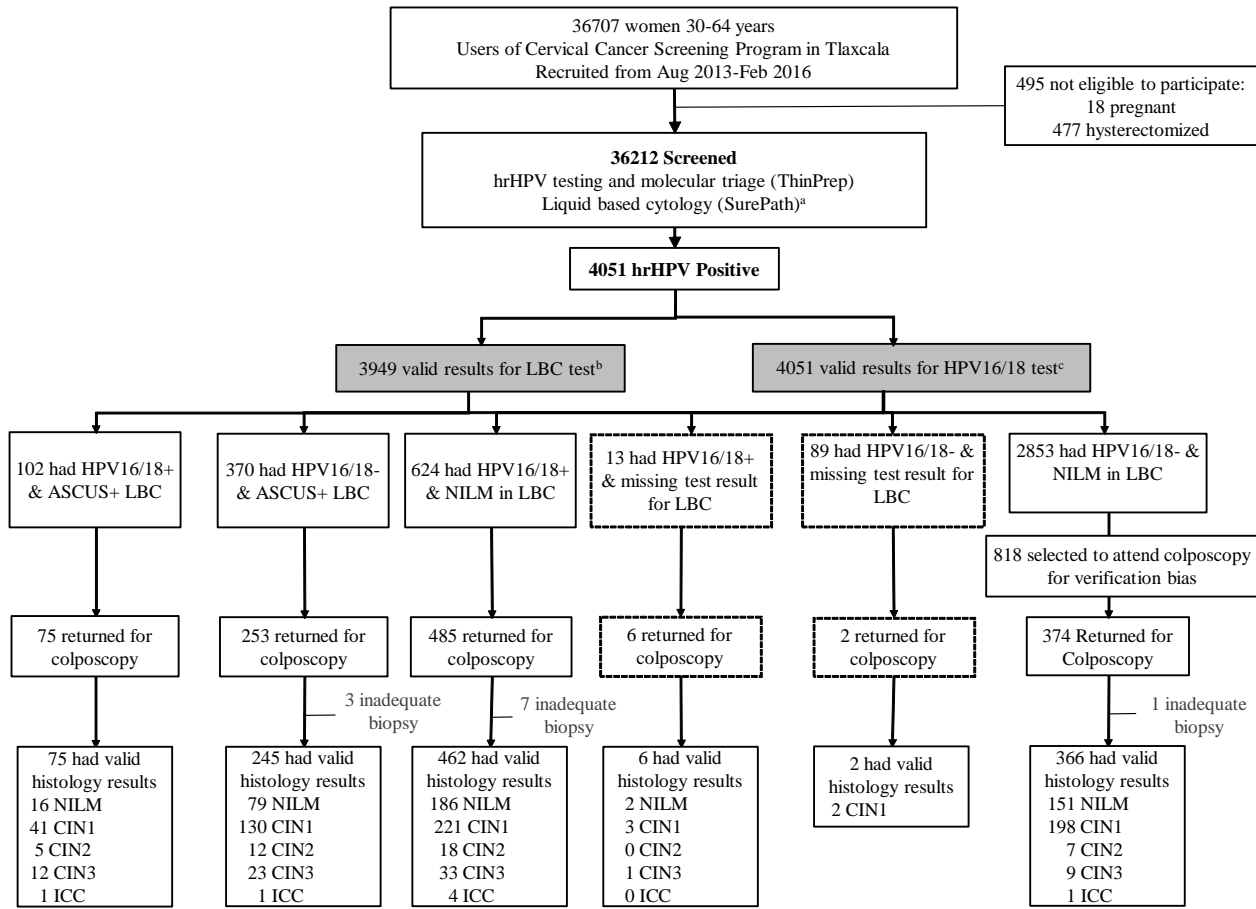
Abbreviation: hrHPV, high-risk human papilloma virus; LBC, Liquid-based cytology; CIN2+, cervical intraepithelial neoplasia grade 2 or worst. <sup>a</sup>p-value McNemar asymptotic when the frequency of discordant pairs is greater than 10, otherwise McNemar exact is reported. <sup>b</sup>McNemar mid-p test. Note: The number of histological outcomes differs by each combination of triage tests according to the availability of valid complete results of them. For instance, there were 102 women hrHPV+ with missing LBC results: 10 had an inadequate specimen and 92 with results not available. There were 3 samples with invalid results for HPV16 genotyping but with valid results for HPV18, therefore they met the criteria to colposcopy referral (positive infection for HPV16 and/or HPV18).

**eTable 2.** Characteristics of Women With Negative or Normal Triage Test Results  
Women Stratified by Receipt of Disease Verification by Histopathological Examination  
to Adjust for Verification Bias

| Characteristics  |                    | Total triage<br>negative<br>(N=2853) <sup>a</sup> | Control group<br>Verified<br>n=366 <sup>b</sup><br>(12.8%) | No verified<br>n=2,487 (87.2%) | p-value <sup>c</sup> |
|--|--------------------|---|--|--------------------------------|----------------------|
|  |                    | % (No.)   | % (95% CI)   | % (95% CI)                     |                      |
| <b>Age (years)</b>                                     |                    |   |  |                                |                      |
|  | Median (IQR)       | 39 (34-47)  | 39 (34-46)   | 39 (34-48)                     | .39                  |
|  | 30-34              | 27.6 (788)  | 29.2 (24.6-33.9)   | 27.4 (25.6-29.1)               | .46                  |
|  | 35-39              | 23.0 (657)  | 24.6 (20.2-29.0)   | 22.8 (21.1-24.4)               | .45                  |
|  | 40-44              | 17.0 (484)  | 16.9 (13.1-20.8)   | 17.0 (15.5-18.4)               | >.99                 |
|  | 45-49              | 11.6 (330)  | 10.9 (7.7-14.1)  | 11.7 (10.4-12.9)               | .68                  |
|  | 50-54              | 9.9 (282)   | 8.7 (5.8-11.6)   | 10.1 (8.9-11.2)                | .43                  |
|  | 55-59              | 7.4 (210)   | 6.6 (4.0-9.1)  | 7.5 (6.4-8.5)                  | .53                  |
|  | 60-64              | 3.6 (102)   | 3.0 (1.3-4.8)  | 3.7 (2.9-4.4)                  | .53                  |
| <b>Age of sexual debut (years)</b>                     |                    |   |  |                                |                      |
|  | Median (IQR)       | 18 (16-20)  | 18 (16-20)   | 18 (16-20)                     | .59                  |
| <b>Number of Lifetime sexual partners</b>              |                    |   |  |                                |                      |
|  | Median (IQR)       | 1 (1-2)   | 1 (1-2)  | 1 (1-2)                        | .12                  |
|  | 1 partner          | 57.8 (1649)                                       | 53.5 (48.4-58.7)   | 58.4 (56.5-60.4)               | .078                 |
|  | 2 partners         | 25.5 (726)  | 29.0 (24.3-33.6)   | 24.9 (23.2-26.6)               | .098                 |
|  | 3-5 partners       | 15.1 (432)  | 15.6 (11.9-19.3)   | 15.1 (13.7-16.5)               | .80                  |
|  | 6 or more partners | 1.6 (46)  | 1.9 (0.5-3.3)  | 1.6 (1.1-2.1)                  | .62                  |
| <b>Number of sexual partners in the last 12 months</b> |                    |   |  |                                |                      |
|  | 0 partners         | 20.4 (583)  | 22.5 (18.1-26.9)   | 20.1 (18.6-21.7)               | .31                  |
|  | 1 partner          | 78.5 (2239)                                       | 77.2 (72.7-81.6)   | 78.6 (77.0-80.3)               | .54                  |
|  | 2 or more          | 1.0 (27)  | 0.29 (-0.3-0.9)  | 1.0 (.6-1.4)                   | .18                  |
|  | Missing            | 0.1 (4)   | 0  | 0.2 (0.0-0.3)                  | .46                  |
| <b>Number of pregnancies</b>                           |                    |   |  |                                |                      |
|  | Median (IQR)       | 3 (2-5)   | 3 (2-5)  | 3 (2-5)                        | .025                 |
|  | None               | 3.4 (96)  | 3.8 (1.9-5.8)  | 3.3 (2.6-4.0)                  | .60                  |
|  | 1-2                | 26.6 (759)  | 30.9 (26.1-35.6)   | 26.0 (24.2-27.7)               | .048                 |
|  | 3-4                | 44.4 (1266)                                       | 44.3 (39.2-49.3)   | 44.4 (42.4-46.3)               | .96                  |
|  | 5-9                | 24.1 (687)  | 19.7 (15.6-23.7)   | 24.7 (23.0-26.4)               | .035                 |
|  | 10 or more         | 1.5 (44)  | 1.4 (0.2-2.5)  | 1.6 (1.1-2.0)                  | .77                  |
| <b>Number of vaginal deliveries</b>                    |                    |   |  |                                |                      |
|  | None               | 25.8 (736)  | 28.1 (23.5-32.7)   | 25.4 (23.7-27.2)               | .27                  |
|  | 1-2                | 28.9 (798)  | 29.8 (25.1-34.5)   | 27.7 (25.9-29.5)               | .41                  |
|  | 3-5                | 36.7 (1047)                                       | 33.6 (28.8-38.4)   | 37.1 (35.2-39.0)               | .19                  |
|  | 6 or more          | 9.5 (271)   | 8.5 (5.6-11.3)   | 9.6 (8.5-10.8)                 | .47                  |
| <b>History of Hormonal Contraception</b>               |                    |   |  |                                |                      |
|  | No                 | 77.0 (2196)                                       | 80.9 (76.8-84.9)   | 76.4 (74.7-78.1)               | .057                 |
|  | Yes                | 22.7 (647)  | 19.1 (15.1-23.1)   | 23.2 (21.5-24.8)               | .082                 |
|  | Missing            | 0.3 (10)  | 0  | 0.4 (0.1-0.6)                  | .22                  |
| <b>Condom use</b>                                      |                    |   |  |                                |                      |
|  | Never              | 78.6 (2242)                                       | 78.7 (74.5-82.9)   | 78.6 (76.9-80.2)               | .96                  |
|  | Almost always      | 10.9 (312)  | 10.6 (7.5-13.8)  | 11.0 (9.7-12.2)                | .85                  |

|  |         |             |                  |                  |      |
|--|---------|-------------|------------------|------------------|------|
|  | Always  | 7.6 (216)   | 7.1 (4.5-9.7)    | 7.6 (6.6-8.7)    | .72  |
|  | Missing | 2.9 (83)    | 3.5 (1.6-5.4)    | 2.8 (2.2-3.5)    | .43  |
| Tobacco use  |         |             |                  |                  |      |
|  | Never   | 94.4 (2693) | 96.2 (94.2-98.1) | 94.1 (93.2-95.0) | .11  |
|  | Former  | 1.3 (37)    | 0.8 (-0.1-1.7)   | 1.4 (0.9-1.8)    | .39  |
|  | Current | 3.6 (103)   | 2.5 (0.9-4.0)    | 3.8 (3.0-4.5)    | .21  |
|  | Missing | 0.7 (20)    | 0.5 (-0.2-1.3)   | 0.7 (0.4-1.0)    | .70  |
| History of Previous HPV screening  |         |             |                  |                  |      |
|  | Never   | 69.7 (1989) | 68.8 (64.1-73.6) | 69.8 (68.0-71.6) | .70  |
|  | Yes     | 28.0 (798)  | 29.8 (25.1-34.5) | 27.7 (25.9-29.5) | .41  |
|  | Missing | 2.3 (66)    | 1.4 (0.2-2.5)    | 2.4 (1.8-3.1)    | .20  |
| History of Previous Pap screening  |         |             |                  |                  |      |
|  | Never   | 23.0 (655)  | 25.1 (20.7-29.6) | 22.6 (21.0-24.3) | .29  |
|  | Yes     | 75.7 (2159) | 72.4 (67.8-77.0) | 76.1 (74.5-77.8) | .12  |
|  | Missing | 1.4 (39)    | 2.5 (0.9-4.0)    | 1.2 (0.8-1.6)    | .054 |
| History of previous cervical cancer screening  |         |             |                  |                  |      |
|  | Never   | 21.4 (609)  | 22.4 (18.1-26.7) | 21.2 (19.6-22.8) | .60  |
|  | Yes     | 77.4 (2207) | 75.1 (70.7-79.6) | 77.7 (76.0-79.3) | .28  |
|  | Missing | 1.3 (37)    | 2.5 (0.9-4.0)    | 1.1 (0.7-1.5)    | .035 |
| <sup>a</sup> All HPV+ women with double negative triage tests results (negative to HPV16/18 tests and normal in cytology). <sup>b</sup> Subsample of women negative to LBC and HPV16/18 genotyping tests who receive disease verification used for correction of verification bias. <sup>c</sup> p-value two sample test of proportions for categorical variables or Two-sample Wilcoxon rank-sum (Mann-Whitney) test for continuous data. |         |             |                  |                  |      |

**eFigure. STARD Diagram**



This flowchart represents the study design used to evaluate HPV16/18 genotyping and liquid-based cytology as triage tests using the baseline results of the first screening round of the FRIDA study trial. Abbreviation: hrHPV, high-risk human papilloma virus; LBC, Liquid-based cytology; NILM, negative for intraepithelial lesion or malignancy, ASCUS+, Atypical squamous cells of undetermined significance or worse; CIN, cervical intraepithelial neoplasia; ICC, invasive cervical cancer.

<sup>a</sup>Sample placed in SurePath vial was only used to perform LBC in hrHPV positive women. <sup>b</sup>Although by protocol all hrHPV positive women should had been tested by LBC, valid LBC results were available only in 97.7% of hrHPV positive women. There were 102 hrHPV+ women with missing LBC results: 10 had an inadequate specimen and 92 did not have available results. <sup>c</sup>There were 3 samples with invalid results for HPV16 genotyping but with valid results for HPV18, therefore they met the criteria for colposcopy referral (positive infection for HPV16 and/or HPV18). Positive for HPV16/18 is indicated by HPV16/18+. Negatives for HPV16/18 are indicated by HPV16/18-. The boxes with dotted lines depict the women who were part of the HPV16/18 performance evaluation but who were excluded from the triage approach based on LBC.