Clinical Validation of p16/Ki-67 Dual-Stained Cytology Triage of HPV-Positive Women – Results from the IMPACT Trial

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Supplementary Materials

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Supplementary Figure 1. Flow of subjects through baseline and follow-up phases of the IMPACT trial

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Supplementary Figure 3. Risk of ≥CIN3 in cobas 4800 HPV-positive women dependent on HPV genotype group, cytology, and Dual-stain results
### Supplementary Table 1. Demographic characteristics and HPV vaccination status by Dual-stain results of the cobas 6800/8800 HPV-positive study population

| Demographic Characteristic | Dual-stain Results |  |
|----------------------------|--------------------|--|
|                            | Positive (N=2382)  | Negative (N=2545) | Invalid (N=323) | Total (N=5250) |
| Age                        |                    |                    |                  |
| Mean (SD)                  | 36.5 (10.4)        | 37.5 (10.2)        | 37.5 (10.5)      | 37.1 (10.3)    |
| Median                     | 33.0               | 35.0               | 34.0             | 34.0           |
| Min, Max                   | 25.0, 65.0         | 25.0, 65.0         | 25.0, 64.0       | 25.0, 65.0     |
| Age group                  |                    |                    |                  |
| 25-29                      | 776 (49.5)         | 700 (44.6)         | 92 (5.9)         | 1568 (29.9)    |
| 30-39                      | 884 (45.5)         | 941 (48.4)         | 119 (6.1)        | 1944 (37.0)    |
| 40-49                      | 351 (38.4)         | 501 (54.8)         | 62 (6.8)         | 914 (17.4)     |
| 50-59                      | 278 (43.9)         | 320 (50.6)         | 35 (5.5)         | 633 (12.1)     |
| 60-65                      | 93 (48.7)          | 83 (45.5)          | 15 (7.9)         | 191 (3.6)      |
| Ethnicity                  |                    |                    |                  |
| Hispanic or Latino         | 672 (49.7)         | 619 (45.8)         | 62 (4.6)         | 1353 (25.8)    |
| Not Hispanic or Latino     | 1688 (43.9)        | 1897 (49.4)        | 257 (6.7)        | 3842 (73.2)    |
| Unknown                    | 9 (45.0)           | 11 (55.0)          | 0 (0.0)          | 20 (0.4)       |
| Not Reported               | 13 (37.1)          | 18 (51.4)          | 4 (11.4)         | 35 (0.7)       |
| Race                       |                    |                    |                  |
| American Indian/Alaskan Native | 12 (40.0)     | 15 (50.0)          | 3 (10.0)         | 30 (0.6)       |
| Asian                      | 46 (43.8)          | 47 (44.8)          | 12 (11.4)        | 105 (2.0)      |
| Black/African-American     | 571 (42.1)         | 687 (50.7)         | 97 (7.2)         | 1355 (25.8)    |
| Native Hawaiian/Pacific Islander | 6 (46.2)   | 7 (53.8)           | 0 (0.0)          | 13 (0.2)       |
| White                      | 1653 (46.9)        | 1682 (47.7)        | 193 (5.5)        | 3528 (67.2)    |
| Other                      | 62 (41.1)          | 78 (51.7)          | 11 (7.3)         | 151 (2.9)      |
| Unknown/Not Reported        | 32 (47.1)          | 29 (42.6)          | 7 (10.3)         | 68 (1.3)       |
| Vaccination status         |                    |                    |                  |
| HPV Vaccine                |                    |                    |                  |
| No                         | 1997 (45.4)        | 2130 (48.4)        | 275 (6.2)        | 4402 (83.8)    |
| Missing                    | 1 (100.0)          | 0 (0.0)            | 0 (0.0)          | 1 (0.0)        |
| Yes                        | 384 (45.3)         | 415 (49.0)         | 48 (5.7)         | 847 (16.1)     |
| Type of vaccine            |                    |                    |                  |
| Gardasil                   | 305 (45.1)         | 333 (49.3)         | 38 (5.6)         | 676 (79.8)     |
| Gardasil 9                 | 9 (60.0)           | 6 (40.0)           | 0 (0.0)          | 15 (1.8)       |
| Cervarix                   | 1 (50.0)           | 1 (50.0)           | 0 (0.0)          | 2 (0.2)        |
| Unknown                    | 69 (44.8)          | 75 (48.7)          | 10 (6.5)         | 154 (18.2)     |

Invalid Dual-stain results include unsatisfactory test results and negative test results with invalid run controls. Row percentage is calculated for each Dual-stain category, column percentage is calculated for total.
**Supplementary Table 2.** HPV genotype and Dual-stain results by baseline cytology and cumulative 1-year histology results among cobas 6800/8800 HPV-positive women

| Cytologic Test Result | Cumulative 1-Year CPR Histology Result | Subject n (%) |
|-----------------------|----------------------------------------|---------------|
|                       | Total (n=4927)                         | Unavailable* (n=966) | NILM (n=2906) | CIN1 (n=423) | CIN2 (n=364) | CIN3 (n=245) | ACIS (n=16) | Cancer (n=7) |
| NILM                  | 3090 (62.7)                            | 634 (65.6)     | 2061 (70.9)  | 169 (40.0)  | 149 (40.9)  | 69 (28.2)   | 7 (43.8)    | 1 (14.3)     |
| HPV16+ and DS+        | 194 (33.2)                             | 36 (32.7)      | 105 (26.7)   | 14 (45.2)   | 16 (80.0)   | 22 (73.3)   | 0           | 1 (100.0)    |
| HPV16+ and DS-        | 391 (66.8)                             | 74 (67.3)      | 288 (73.3)   | 17 (54.8)   | 4 (20.0)    | 8 (26.7)    | 0           | 0            |
| HPV18+ and DS+        | 86 (27.7)                              | 15 (24.2)      | 56 (26.0)    | 4 (28.6)    | 7 (53.8)    | 2 (100.0)   | 0           | 0            |
| HPV18+ and DS-        | 225 (72.3)                             | 47 (75.8)      | 159 (74.0)   | 10 (71.4)   | 6 (46.2)    | 0           | 0           | 3 (60.0)     |
| 12 Other HPV+ and DS+ | 750 (34.2)                             | 156 (33.8)     | 434 (29.9)   | 57 (46.0)   | 77 (66.4)   | 24 (64.9)   | 0           | 0            |
| 12 Other HPV+ and DS- | 1444 (65.8)                            | 306 (66.2)     | 1019 (70.1)  | 67 (54.0)   | 39 (33.6)   | 13 (35.1)   | 0           | 0            |
| ASC-US                | **812 (16.5)**                         | **138 (14.3)** | **461 (15.9)** | **103 (24.3)** | **70 (19.2)** | **38 (15.5)** | **2 (12.5)** | **0**        |
| HPV16+ and DS+        | 113 (70.2)                             | 25 (78.1)      | 49 (58.3)    | 10 (71.4)   | 13 (92.9)   | 14 (93.3)   | 0           | 0            |
| HPV16+ and DS-        | 48 (29.8)                              | 7 (21.9)       | 35 (41.7)    | 4 (28.6)    | 1 (7.1)     | 1 (6.7)     | 0           | 0            |
| HPV18+ and DS+        | 36 (59.0)                              | 10 (76.9)      | 16 (45.7)    | 4 (66.7)    | 3 (75.0)    | 3 (100.0)   | 0           | 0            |
| HPV18+ and DS-        | 25 (41.0)                              | 3 (23.1)       | 19 (54.3)    | 2 (33.3)    | 1 (25.0)    | 0           | 0           | 0            |
| 12 Other HPV+ and DS+ | 361 (61.2)                             | 58 (62.4)      | 181 (52.9)   | 60 (72.3)   | 44 (84.6)   | 18 (90.0)   | 0           | 0            |
| 12 Other HPV+ and DS- | 229 (38.8)                             | 35 (37.6)      | 161 (47.1)   | 23 (27.7)   | 8 (15.4)    | 2 (10.0)    | 0           | 0            |
| AGC/ASC-H             | **142 (2.9)**                          | **27 (2.8)**   | **35 (1.2)** | **7 (1.7)** | **24 (6.6)** | **40 (16.3)** | **7 (43.8)** | **2 (28.6)** |
| HPV16+ and DS+        | 55 (93.2)                              | 8 (88.9)       | 6 (75.0)     | 4 (100.0)   | 8 (100.0)   | 23 (95.8)   | 5 (100.0)   | 1 (100.0)    |
| HPV16+ and DS-        | 4 (6.8)                                | 1 (11.1)       | 2 (25.0)     | 0           | 0           | 0           | 1 (42.2)    | 0            |
| HPV18+ and DS+        | 16 (94.1)                              | 4 (100.0)      | 4 (80.0)     | 1 (100.0)   | 2 (100.0)   | 2 (100.0)   | 2 (100.0)   | 1 (100.0)    |
| HPV18+ and DS-        | 1 (5.9)                                | 0              | 1 (20.0)     | 0           | 0           | 0           | 0           | 0            |
| 12 Other HPV+ and DS+ | 58 (87.9)                              | 13 (92.9)      | 16 (72.7)    | 2 (100.0)   | 13 (92.9)   | 14 (100.0)  | 0           | 0            |
| 12 Other HPV+ and DS- | 8 (12.1)                               | 1 (7.1)        | 6 (27.3)     | 0           | 1 (7.1)     | 0           | 0           | 0            |
| LSIL                  | **728 (14.8)**                         | **140 (14.5)** | **310 (10.7)** | **135 (31.9)** | **99 (27.2)** | **43 (17.6)** | **0**       | **1 (14.3)** |
| HPV16+ and DS+        | 121 (89.0)                             | 22 (88.0)      | 34 (87.2)    | 17 (77.3)   | 28 (93.3)   | 20 (100.0)  | 0           | 0            |
| HPV16+ and DS-        | 15 (11.0)                              | 3 (12.0)       | 5 (12.8)     | 5 (22.7)    | 2 (6.7)     | 0           | 0           | 0            |
| HPV18+ and DS+        | 44 (77.2)                              | 7 (77.8)       | 13 (68.4)    | 12 (80.0)   | 8 (88.9)    | 4 (80.0)    | 0           | 0            |
| HPV18+ and DS-        | 13 (22.8)                              | 2 (22.2)       | 6 (31.6)     | 3 (20.0)    | 1 (11.1)    | 1 (20.0)    | 0           | 0            |
| 12 Other HPV+ and DS+ | 410 (76.6)                             | 83 (78.3)      | 169 (67.1)   | 83 (84.7)   | 56 (93.3)   | 18 (100.0)  | 0           | 1 (100.0)    |
| 12 Other HPV+ and DS- | 125 (23.4)                             | 23 (21.7)      | 83 (32.9)    | 15 (15.3)   | 4 (6.7)     | 0           | 0           | 0            |
| Cytologic Test Result | Total (n=4927) | Unavailable* (n=966) | NILM (n=2906) | CIN1 (n=423) | CIN2 (n=364) | CIN3 (n=245) | ACIS (n=16) | Cancer (n=7) |
|-----------------------|----------------|----------------------|--------------|-------------|-------------|-------------|-------------|-------------|
| HSIL/ACIS             | 118 (2.4)      | 15 (1.6)             | 19 (0.7)     | 7 (1.7)     | 19 (5.2)    | 55 (22.4)   | 0           | 3 (42.9)    |
| HPV16+ and DS+        | 51 (100.0)     | 3 (100.0)            | 6 (100.0)    | 2 (100.0)   | 6 (100.0)   | 32 (100.0)  | 0           | 2 (100.0)   |
| HPV16+ and DS-        | 0              | 0                    | 0            | 0           | 0           | 0           | 0           | 0           |
| HPV18+ and DS+        | 10 (100.0)     | 2 (100.0)            | 2 (100.0)    | 1 (100.0)   | 1 (100.0)   | 3 (100.0)   | 0           | 1 (100.0)   |
| HPV18+ and DS-        | 0              | 0                    | 0            | 0           | 0           | 0           | 0           | 0           |
| 12 Other HPV+ and DS+ | 53 (93.0)      | 9 (90.0)             | 9 (81.8)     | 4 (100.0)   | 11 (91.7)   | 20 (100.0)  | 0           | 0           |
| 12 Other HPV+ and DS- | 4 (7.0)        | 1 (10.0)             | 2 (18.2)     | 0           | 1 (8.3)     | 0           | 0           | 0           |
| Unavailable           | 37 (0.8)       | 12 (1.2)             | 20 (0.7)     | 2 (0.5)     | 3 (0.8)     | 0           | 0           | 0           |
| HPV16+ and DS+        | 6 (85.7)       | 4 (100.0)            | 1 (50.0)     | 0           | 1 (100.0)   | 0           | 0           | 0           |
| HPV16+ and DS-        | 1 (14.3)       | 0                    | 1 (50.0)     | 0           | 0           | 0           | 0           | 0           |
| HPV18+ and DS+        | 3 (75.0)       | 2 (100.0)            | 1 (100.0)    | 0           | 0           | 0           | 0           | 0           |
| HPV18+ and DS-        | 1 (25.0)       | 0                    | 0            | 0           | 1 (100.0)   | 0           | 0           | 0           |
| 12 Other HPV+ and DS+ | 15 (57.7)      | 4 (66.7)             | 9 (52.9)     | 2 (100.0)   | 0           | 0           | 0           | 0           |
| 12 Other HPV+ and DS- | 11 (42.3)      | 2 (33.3)             | 8 (47.1)     | 0           | 1 (100.0)   | 0           | 0           | 0           |
| Total                 | 4927 (100.0)   | 966 (100.0)          | 2906 (100.0) | 423 (100.0) | 364 (100.0) | 245 (100.0) | 16 (100.0)  | 7 (100.0)   |
| HPV16+ and DS+        | 540 (54.1)     | 98 (53.6)            | 201 (37.8)   | 47 (64.4)   | 72 (91.1)   | 111 (91.7)  | 7 (100.0)   | 4 (100.0)   |
| HPV16+ and DS-        | 459 (45.9)     | 85 (46.4)            | 331 (62.2)   | 26 (35.6)   | 7 (8.9)     | 10 (8.3)    | 0           | 0           |
| HPV18+ and DS+        | 195 (42.4)     | 40 (43.5)            | 92 (33.2)    | 22 (59.5)   | 21 (70.0)   | 14 (93.3)   | 4 (57.1)    | 2 (100.0)   |
| HPV18+ and DS-        | 265 (57.6)     | 52 (56.5)            | 185 (66.8)   | 15 (40.5)   | 9 (30.0)    | 1 (6.7)     | 3 (42.9)    | 0           |
| 12 Other HPV+ and DS+ | 1647 (47.5)    | 323 (46.7)           | 818 (39.0)   | 208 (66.5)  | 201 (78.8)  | 94 (86.2)   | 2 (100.0)   | 1 (100.0)   |
| 12 Other HPV+ and DS- | 1821 (52.5)    | 368 (53.3)           | 1279 (61.0)  | 105 (33.5)  | 54 (21.2)   | 15 (13.8)   | 0           | 0           |

*Out of 966 cases with CPR results marked as "Unavailable", 38 cases had inadequate CPR results, 111 cases had invalid CPR results due to the biopsies collected outside of the study visit window, and 817 cases had no biopsy collected for CPR diagnosis.

Percentages at the top rows of each cytology category (bolded) are column percentages with respect to that cytology category. Other percentages are column percentages with respect to the corresponding HPV genotype group. DS, Dual-stain; CPR, central pathology review; NILM, negative for intraepithelial lesion or malignancy; ASC-US, atypical squamous cells of undetermined significance; AGC/ASC-H, atypical glandular cells/atypical squamous cells - cannot exclude HSIL; LSIL, low-grade squamous intraepithelial lesions; HSIL, high-grade squamous intraepithelial lesions; ACIS, adenocarcinoma in-situ; CIN, cervical intraepithelial neoplasia
**Supplementary Table 3.** HPV genotype and Dual-stain results by cytology and baseline histology results among cobas 4800 HPV-positive women

| Cytologic Test Result | Total (n=4727) | Unavailable* (n=975) | NILM (n=2864) | CIN1 (n=352) | CIN2 (n=310) | CIN3 (n=208) | ACIS (n=11) | Cancer (n=7) |
|-----------------------|----------------|-----------------------|---------------|--------------|--------------|--------------|-------------|-------------|
| NILM                  | 2901 (61.4)    | 631 (64.7)            | 1964 (68.6)   | 125 (35.5)   | 122 (39.4)   | 54 (26.0)    | 4 (36.4)    | 1 (14.3)    |
| HPV16+ and DS+        | 167 (46.1)     | 33 (44.6)             | 86 (38.2)     | 12 (63.2)    | 16 (84.2)    | 19 (79.2)    | 0           | 1 (100.0)   |
| HPV16+ and DS-        | 195 (53.9)     | 41 (55.4)             | 139 (61.8)    | 7 (36.8)     | 3 (15.8)     | 5 (20.8)     | 0           | 0           |
| HPV18+ and DS+        | 54 (36.0)      | 9 (40.9)              | 36 (32.1)     | 2 (28.6)     | 5 (83.3)     | 1 (100.0)    | 1 (50.0)    | 0           |
| HPV18+ and DS-        | 96 (64.0)      | 13 (59.1)             | 76 (67.9)     | 5 (71.4)     | 1 (16.7)     | 0            | 1 (50.0)    | 0           |
| 12 Other HPV+ and DS+ | 775 (32.4)     | 175 (32.7)            | 467 (28.7)    | 48 (48.5)    | 65 (67.0)    | 18 (62.1)    | 2 (100.0)   | 0           |
| 12 Other HPV+ and DS- | 1614 (67.6)    | 360 (67.3)            | 1160 (71.3)   | 51 (51.5)    | 32 (33.0)    | 11 (37.9)    | 0           | 0           |
| ASC-US                | 792 (16.8)     | 137 (14.1)            | 473 (16.5)    | 87 (24.7)    | 63 (20.3)    | 31 (14.9)    | 1 (9.1)     | 0           |
| HPV16+ and DS+        | 99 (75.6)      | 24 (82.8)             | 44 (64.7)     | 5 (71.4)     | 13 (100.0)   | 12 (92.3)    | 1 (100.0)   | 0           |
| HPV16+ and DS-        | 32 (24.4)      | 5 (17.2)              | 24 (35.3)     | 2 (28.6)     | 0            | 1 (7.7)      | 0           | 0           |
| HPV18+ and DS+        | 25 (61.0)      | 7 (77.8)              | 10 (47.6)     | 4 (57.1)     | 2 (100.0)    | 2 (100.0)    | 0           | 0           |
| HPV18+ and DS-        | 16 (39.0)      | 2 (22.2)              | 11 (52.4)     | 3 (42.9)     | 0            | 0            | 0           | 0           |
| 12 Other HPV+ and DS+ | 372 (60.0)     | 63 (63.6)             | 195 (50.8)    | 57 (78.1)    | 43 (89.6)    | 14 (87.5)    | 0           | 0           |
| 12 Other HPV+ and DS- | 248 (40.0)     | 36 (36.4)             | 189 (49.2)    | 16 (21.9)    | 5 (10.4)     | 2 (12.5)     | 0           | 0           |
| AGC/ASC-H             | 141 (3.0)      | 26 (2.7)              | 46 (16.6)     | 4 (1.1)      | 19 (6.1)     | 38 (18.3)    | 6 (54.5)    | 2 (28.6)    |
| HPV16+ and DS+        | 55 (96.5)      | 8 (100.0)             | 12 (92.3)     | 3 (100.0)    | 5 (100.0)    | 21 (95.5)    | 5 (100.0)   | 1 (100.0)   |
| HPV16+ and DS-        | 2 (3.5)        | 0                    | 1 (7.7)       | 0            | 0            | 1 (4.5)      | 0           | 0           |
| HPV18+ and DS+        | 15 (100.0)     | 4 (100.0)             | 6 (100.0)     | 0            | 2 (100.0)    | 1 (100.0)    | 1 (100.0)   | 1 (100.0)   |
| HPV18+ and DS-        | 0              | 0                    | 0             | 0            | 0            | 0            | 0           | 0           |
| 12 Other HPV+ and DS+ | 60 (87.0)      | 13 (92.9)             | 21 (77.8)     | 1 (100.0)    | 10 (83.3)    | 15 (100.0)   | 0           | 0           |
| 12 Other HPV+ and DS- | 9 (13.0)       | 1 (7.1)               | 6 (22.2)      | 0            | 2 (16.7)     | 0            | 0           | 0           |
| LSIL                  | 733 (15.5)     | 153 (15.7)            | 335 (11.7)    | 129 (36.6)   | 84 (27.1)    | 31 (14.9)    | 0           | 1 (14.3)    |
| HPV16+ and DS+        | 118 (88.1)     | 22 (81.5)             | 40 (85.1)     | 14 (87.5)    | 26 (92.9)    | 16 (100.0)   | 0           | 0           |
| HPV16+ and DS-        | 16 (11.9)      | 5 (18.5)              | 7 (14.9)      | 2 (12.5)     | 2 (7.1)      | 0            | 0           | 0           |
| HPV18+ and DS+        | 44 (81.5)      | 9 (90.0)              | 14 (73.7)     | 14 (87.5)    | 5 (83.3)     | 2 (66.7)     | 0           | 0           |
| HPV18+ and DS-        | 10 (18.5)      | 1 (10.0)              | 5 (26.3)      | 2 (12.5)     | 1 (16.7)     | 1 (33.3)     | 0           | 0           |
| 12 Other HPV+ and DS+ | 419 (76.9)     | 89 (76.7)             | 187 (69.5)    | 83 (85.6)    | 47 (94.0)    | 12 (100.0)   | 0           | 1 (100.0)   |
| 12 Other HPV+ and DS- | 126 (23.1)     | 27 (23.3)             | 82 (30.5)     | 14 (14.4)    | 3 (6.0)      | 0           | 0           | 0           |
| Cytologic Test Result | Total (n=4727) | Unavailable* (n=975) | NILM (n=2864) | CIN1 (n=352) | CIN2 (n=310) | CIN3 (n=208) | ACIS (n=11) | Cancer (n=7) |
|----------------------|----------------|----------------------|--------------|-------------|-------------|-------------|------------|-------------|
| HSIL/ACIS            | 118 (2.5)      | 15 (1.5)             | 23 (0.8)     | 5 (1.4)     | 18 (5.8)    | 54 (26.0)   | 0          | 3 (42.9)    |
| HPV16+ and DS+       | 51 (100.0)     | 3 (100.0)            | 7 (100.0)    | 1 (100.0)   | 6 (100.0)   | 32 (100.0)  | 0          | 2 (100.0)   |
| HPV16+ and DS-       | 0              | 0                    | 0            | 0           | 0           | 0           | 0          | 0           |
| HPV18+ and DS+       | 10 (100.0)     | 2 (100.0)            | 2 (100.0)    | 1 (100.0)   | 1 (100.0)   | 3 (100.0)   | 0          | 1 (100.0)   |
| HPV18+ and DS-       | 0              | 0                    | 0            | 0           | 0           | 0           | 0          | 0           |
| 12 Other HPV+ and DS+| 53 (93.0)      | 9 (90.0)             | 12 (85.7)    | 3 (100.0)   | 10 (90.9)   | 19 (100.0)  | 0          | 0           |
| 12 Other HPV+ and DS-| 4 (7.0)        | 1 (10.0)             | 2 (14.3)     | 0           | 1 (9.1)     | 0           | 0          | 0           |
| Unavailable          | 42 (0.9)       | 13 (1.3)             | 23 (0.8)     | 2 (0.6)     | 4 (1.3)     | 0           | 0          | 0           |
| HPV16+ and DS+       | 6 (85.7)       | 4 (100.0)            | 1 (50.0)     | 0           | 1 (100.0)   | 0           | 0          | 0           |
| HPV16+ and DS-       | 1 (14.3)       | 0                    | 1 (50.0)     | 0           | 0           | 0           | 0          | 0           |
| HPV18+ and DS+       | 1 (50.0)       | 1 (100.0)            | 0            | 0           | 0           | 0           | 0          | 0           |
| HPV18+ and DS-       | 1 (50.0)       | 0                    | 0            | 0           | 1 (100.0)   | 0           | 0          | 0           |
| 12 Other HPV+ and DS+| 17 (51.5)      | 5 (62.5)             | 9 (42.9)     | 2 (100.0)   | 1 (50.0)    | 0           | 0          | 0           |
| 12 Other HPV+ and DS-| 16 (48.5)      | 3 (37.5)             | 12 (57.1)    | 0           | 1 (50.0)    | 0           | 0          | 0           |
| Total                | 4727 (100.0)   | 975 (100.0)          | 2864 (100.0) | 352 (100.0) | 310 (100.0) | 208 (100.0) | 11 (100.0) | 7 (100.0)   |
| HPV16+ and DS+       | 496 (66.8)     | 94 (64.8)            | 190 (52.5)   | 35 (76.1)   | 67 (93.1)   | 100 (93.5)  | 6 (100.0)  | 4 (100.0)   |
| HPV16+ and DS-       | 246 (33.2)     | 51 (35.2)            | 172 (47.5)   | 11 (23.9)   | 5 (6.9)     | 7 (6.5)     | 0          | 0           |
| HPV18+ and DS+       | 149 (54.8)     | 32 (66.7)            | 68 (42.5)    | 21 (67.7)   | 15 (83.3)   | 9 (90.0)    | 2 (66.7)   | 2 (100.0)   |
| HPV18+ and DS-       | 123 (45.2)     | 16 (33.3)            | 92 (57.5)    | 10 (32.3)   | 3 (16.7)    | 1 (10.0)    | 1 (33.3)   | 0           |
| 12 Other HPV+ and DS+| 1696 (45.7)    | 354 (45.3)           | 891 (38.0)   | 194 (70.5)  | 176 (80.0)  | 78 (85.7)   | 2 (100.0)  | 1 (100.0)   |
| 12 Other HPV+ and DS-| 2017 (54.3)    | 428 (54.7)           | 1451 (62.0)  | 81 (29.5)   | 44 (20.0)   | 13 (14.3)   | 0          | 0           |

*Out of 975 cases with CPR results marked as "Unavailable", 55 cases had inadequate CPR results, 136 cases had invalid CPR results due to the biopsies collected outside of the study visit window, and 784 cases had no biopsy collected for CPR diagnosis.

Percentages at the top rows of each cytology category (bolded) are column percentages with respect to that cytology category. Other percentages are column percentages with respect to the corresponding HPV genotype group. DS, Dual-stain; CPR, central pathology review; NILM, negative for intraepithelial lesion or malignancy; ASC-US, atypical squamous cells of undetermined significance; AGC/ASC-H, atypical glandular cells/atypical squamous cells - cannot exclude HSIL; LSIL, low-grade squamous intraepithelial lesions; HSIL, high-grade squamous intraepithelial lesions; ACIS, adenocarcinoma in-situ; CIN, cervical intraepithelial neoplasia
**Supplementary Table 4. HPV genotype and Dual-stain results by baseline Pap cytology and cumulative 1-year histology results among cobas 4800 HPV-positive women**

| Cytologic Test Result | Total (n=4727) | Unavailable* (n=933) | NILM (n=2749) | CIN1 (n=415) | CIN2 (n=366) | CIN3 (n=243) | ACIS (n=14) | Cancer (n=7) |
|-----------------------|----------------|----------------------|----------------|---------------|---------------|---------------|--------------|--------------|
| **NILM**              |                |                      |                |               |               |               |              |              |
| HPV16+ and DS+        | 2901 (61.4)    | 605 (64.8)           | 1914 (69.6)    | 159 (38.3)    | 150 (41.0)    | 67 (27.6)     | 5 (35.7)     | 1 (14.3)     |
| HPV16+ and DS-        | 195 (53.9)     | 39 (55.7)            | 137 (62.3)     | 10 (43.5)     | 3 (15.0)      | 6 (21.4)      | 0            | 0            |
| HPV18+ and DS+        | 54 (36.0)      | 9 (40.9)             | 31 (30.4)      | 4 (40.0)      | 7 (63.6)      | 2 (100.0)     | 1 (33.3)     | 0            |
| HPV18+ and DS-        | 96 (64.0)      | 13 (59.1)            | 71 (69.6)      | 6 (60.0)      | 4 (36.4)      | 0             | 2 (66.7)     | 0            |
| 12 Other HPV+ and DS+ | 775 (32.4)     | 168 (32.7)           | 449 (28.2)     | 58 (46.0)     | 74 (62.2)     | 24 (64.9)     | 2 (100.0)    | 0            |
| 12 Other HPV+ and DS- | 1614 (67.6)    | 345 (67.3)           | 1143 (71.8)    | 68 (54.0)     | 45 (37.8)     | 13 (35.1)     | 0            | 0            |
| **ASC-US**            |                |                      |                |               |               |               |              |              |
| HPV16+ and DS+        | 792 (16.8)     | 132 (14.1)           | 447 (16.3)     | 105 (25.3)    | 69 (18.9)     | 38 (15.6)     | 1 (7.1)      | 0            |
| HPV16+ and DS-        | 99 (75.6)      | 24 (85.7)            | 40 (63.5)      | 7 (70.0)      | 13 (92.9)     | 14 (93.3)     | 1 (100.0)    | 0            |
| HPV18+ and DS+        | 32 (24.4)      | 14 (43.3)            | 23 (36.5)      | 3 (30.0)      | 1 (7.1)       | 1 (6.7)       | 0            | 0            |
| HPV18+ and DS-        | 25 (61.0)      | 7 (77.8)             | 8 (42.1)       | 5 (62.5)      | 2 (100.0)     | 3 (100.0)     | 0            | 0            |
| 12 Other HPV+ and DS+ | 16 (39.0)      | 22 (22.2)            | 11 (57.9)      | 3 (37.5)      | 0             | 0             | 0            | 0            |
| 12 Other HPV+ and DS- | 372 (60.0)     | 61 (64.2)            | 185 (50.7)     | 62 (71.3)     | 46 (86.8)     | 18 (90.0)     | 0            | 0            |
| **AGC/ASC-H**         |                |                      |                |               |               |               |              |              |
| HPV16+ and DS+        | 141 (3.0)      | 26 (2.8)             | 33 (1.2)       | 7 (1.7)       | 25 (6.8)      | 40 (16.5)     | 8 (57.1)     | 2 (28.6)     |
| HPV16+ and DS-        | 55 (96.5)      | 8 (100.0)            | 7 (87.5)       | 4 (100.0)     | 8 (100.0)     | 22 (95.7)     | 5 (100.0)    | 1 (100.0)    |
| HPV18+ and DS+        | 2 (3.5)        | 0 (12.5)             | 1 (12.5)       | 0             | 1 (4.3)       | 0             | 0            | 0            |
| HPV18+ and DS-        | 15 (100.0)     | 4 (100.0)            | 3 (100.0)      | 1 (100.0)     | 2 (100.0)     | 2 (100.0)     | 2 (100.0)    | 1 (100.0)    |
| 12 Other HPV+ and DS+ | 60 (87.0)      | 13 (92.9)            | 16 (72.7)      | 2 (100.0)     | 13 (86.7)     | 15 (100.0)    | 1 (100.0)    | 0            |
| 12 Other HPV+ and DS- | 9 (13.0)       | 7 (71.1)             | 6 (27.3)       | 0             | 2 (13.3)      | 0             | 0            | 0            |
| **LSIL**              |                |                      |                |               |               |               |              |              |
| HPV16+ and DS+        | 733 (15.5)     | 142 (15.2)           | 313 (11.4)     | 135 (32.5)    | 99 (27.0)     | 43 (17.7)     | 0            | 1 (14.3)     |
| HPV16+ and DS-        | 118 (88.1)     | 22 (84.6)            | 33 (84.6)      | 15 (78.9)     | 28 (93.3)     | 20 (100.0)    | 0            | 0            |
| HPV18+ and DS+        | 16 (11.9)      | 4 (15.4)             | 6 (15.4)       | 4 (21.1)      | 2 (6.7)       | 0             | 0            | 0            |
| HPV18+ and DS-        | 44 (81.5)      | 8 (88.9)             | 12 (70.6)      | 13 (86.7)     | 7 (87.5)      | 4 (80.0)      | 0            | 0            |
| HPV18+ and DS-        | 10 (18.5)      | 1 (11.1)             | 5 (29.4)       | 2 (13.3)      | 1 (12.5)      | 1 (20.0)      | 0            | 0            |
| 12 Other HPV+ and DS+ | 419 (76.9)     | 83 (77.6)            | 175 (68.1)     | 85 (84.2)     | 57 (93.4)     | 18 (100.0)    | 0            | 1 (100.0)    |
| 12 Other HPV+ and DS- | 126 (23.1)     | 24 (22.4)            | 82 (31.9)      | 16 (15.8)     | 4 (6.6)       | 0             | 0            | 0            |
### Cumulative 1-Year CPR Histology Result — Subject n (%)

| Cytologic Test Result | Total (n=4727) | Unavailable* (n=933) | NILM (n=2749) | CIN1 (n=415) | CIN2 (n=366) | CIN3 (n=243) | ACIS (n=14) | Cancer (n=7) |
|-----------------------|----------------|----------------------|----------------|-------------|-------------|-------------|-------------|-------------|
| HSIL/ACIS             | 118 (2.5)      | 15 (1.6)             | 19 (0.7)       | 7 (1.7)     | 19 (5.2)    | 55 (22.6)   | 0           | 3 (42.9)    |
| HPV16+ and DS+       | 51 (100.0)     | 3 (100.0)            | 6 (100.0)      | 2 (100.0)   | 6 (100.0)   | 32 (100.0)  | 0           | 2 (100.0)   |
| HPV16+ and DS-       | 0              | 0                    | 0              | 0           | 0           | 0           | 0           | 0           |
| HPV18+ and DS+       | 10 (100.0)     | 0                    | 2 (100.0)      | 1 (100.0)   | 1 (100.0)   | 3 (100.0)   | 0           | 1 (100.0)   |
| HPV18+ and DS-       | 0              | 0                    | 0              | 0           | 0           | 0           | 0           | 0           |
| 12 Other HPV+ and DS+| 53 (93.0)      | 9 (90.0)             | 9 (81.8)       | 4 (100.0)   | 11 (91.7)   | 20 (100.0)  | 0           | 0           |
| 12 Other HPV+ and DS-| 4 (7.0)        | 1 (10.0)             | 2 (18.2)       | 0           | 1 (8.3)     | 0           | 0           | 0           |
| **Unavailable**      | **42 (0.9)**   | **13 (1.4)**         | **23 (0.8)**   | **2 (0.5)** | **4 (1.1)** | 0           | 0           | 0           |
| HPV16+ and DS+       | 6 (85.7)       | 4 (100.0)            | 1 (50.0)       | 0           | 1 (100.0)   | 0           | 0           | 0           |
| HPV16+ and DS-       | 1 (14.3)       | 0                    | 1 (50.0)       | 0           | 0           | 0           | 0           | 0           |
| HPV18+ and DS+       | 1 (50.0)       | 1 (100.0)            | 0              | 0           | 0           | 0           | 0           | 0           |
| HPV18+ and DS-       | 1 (50.0)       | 0                    | 0              | 0           | 1 (100.0)   | 0           | 0           | 0           |
| 12 Other HPV+ and DS+| 17 (51.5)      | 5 (62.5)             | 9 (42.9)       | 2 (100.0)   | 1 (50.0)    | 0           | 0           | 0           |
| 12 Other HPV+ and DS-| 16 (48.5)      | 3 (37.5)             | 12 (57.1)      | 0           | 1 (50.0)    | 0           | 0           | 0           |
| **Total**            | **4727 (100.0)**| **933 (100.0)**      | **2749 (100.0)**| **415 (100.0)**| **366 (100.0)**| **243 (100.0)**| **14 (100.0)**| **7 (100.0)**|
| HPV16+ and DS+       | 496 (66.8)     | 92 (66.2)            | 170 (50.3)     | 41 (70.7)   | 73 (92.4)   | 110 (93.2)  | 6 (100.0)   | 4 (100.0)   |
| HPV16+ and DS-       | 246 (33.2)     | 47 (33.8)            | 168 (49.7)     | 17 (29.3)   | 6 (7.6)     | 8 (6.8)     | 0           | 0           |
| HPV18+ and DS+       | 149 (54.8)     | 31 (66.0)            | 56 (39.2)      | 24 (68.6)   | 19 (76.0)   | 14 (93.3)   | 3 (60.0)    | 2 (100.0)   |
| HPV18+ and DS-       | 123 (45.2)     | 16 (34.0)            | 87 (60.8)      | 11 (31.4)   | 6 (24.0)    | 1 (6.7)     | 2 (40.0)    | 0           |
| 12 Other HPV+ and DS+| 1696 (45.7)    | 339 (45.4)           | 843 (37.2)     | 213 (66.1)  | 202 (77.1)  | 95 (86.4)   | 3 (100.0)   | 1 (100.0)   |
| 12 Other HPV+ and DS-| 2017 (54.3)    | 408 (54.6)           | 1425 (62.8)    | 109 (33.9)  | 60 (22.9)   | 15 (13.6)   | 0           | 0           |

*Out of 933 cases with CPR results marked as "Unavailable", 37 cases had inadequate CPR results, 112 cases had invalid CPR results due to the biopsies collected outside of the study visit window, and 784 cases had no biopsy collected for CPR diagnosis.

Percentages at the top rows of each cytology category (bolded) are column percentages with respect to that cytology category. Other percentages are column percentages with respect to the corresponding HPV genotype group. DS, Dual-stain; CPR, central pathology review; NILM, negative for intraepithelial lesion or malignancy; ASC-US, atypical squamous cells of undetermined significance; AGC/ASC-H, atypical glandular cells/atypical squamous cells - cannot exclude HSIL; LSIL, low-grade squamous intraepithelial lesions; HSIL, high-grade squamous intraepithelial lesions; ACIS, adenocarcinoma in-situ; CIN, cervical intraepithelial neoplasia.
### Supplementary Table 5. Triage of cobas 4800 HPV-positive women with Dual-stain and cytology by HPV genotype group: baseline and cumulative 1-year data for ≥CIN2 and ≥CIN3

| Disease status | HPV Status | Triage with | Sensitivity % (n/N) | Specificity % (n/N) | PPV % (n/N) | 1-NPV % (n/N) | Positivity rate % (n/N) | Number of baseline colpos per disease detected |
|----------------|------------|-------------|---------------------|---------------------|-------------|--------------|------------------------|--------------------------------------------|
| ≥CIN2          | HPV16/18+  | DS          | 92.7 (204/220)      | 91.3 (230/252)      | 47.6 (284/597) | 49.3 (282/572) | 39.5 (204/517)          | 44.2 (230/520)                              | 5.3 (16/300)                              | 7.2 (22/304)                               | 63.3 (517/817)                             | 2.53 (517/204)                            |
|                |            | Cytoplogy   | 75.9 (167/220)      | 74.2 (187/252)      | 60.8 (363/597) | 62.1 (355/572) | 41.6 (167/401)          | 46.3 (187/404)                              | 12.7 (10.2)                               | 15.5 (12.8)                               | 49.1 (53/416)                             | 2.40 (401/167)                            |
|                | HPV16+     | DS          | 93.6 (176/188)      | 93.2 (192/206)      | 44.8 (182/406) | 46.7 (184/394) | 44.0 (176/400)          | 47.8 (192/402)                              | 6.2 (3.6)                                 | 7.1 (4.3)                                 | 67.3 (400/594)                            | 2.27 (400/176)                            |
|                |            | Cytoplogy   | 76.6 (144/188)      | 76.2 (157/206)      | 60.1 (244/406) | 61.7 (243/394) | 47.1 (144/306)          | 51.0 (157/308)                              | 15.3 (12.0)                               | 16.8 (13.4)                               | 51.5 (444/288)                            | 2.13 (306/144)                            |
|                | HPV18+     | DS          | 87.5 (28/32)        | 82.6 (38/46)        | 53.4 (102/191) | 55.1 (98/178) | 23.9 (28/117)           | 32.2 (38/118)                               | 3.8 (4/106)                                | 7.5 (8/106)                               | 52.5 (117/223)                            | 4.18 (117/28)                             |
|                |            | Cytoplogy   | 71.9 (71/95)        | 65.2 (69/90.9)      | 62.3 (46/60.3) | 62.9 (47/62.2) | 24.2 (19/26.7)          | 31.3 (27/56.8)                              | 7.0 (1.5)                                 | 12.5 (4.0)                                | 42.6 (46/288)                             | 4.13 (46/132)                             |
|                | 12 Other   | DS          | 82.1 (256/312)      | 80.2 (300/374)      | 58.6 (1520/2594)| 59.3 (1522/2567) | 19.2 (256/1330)         | 22.3 (300/1345)                             | 3.6 (56/1756)                              | 4.6 (74/1596)                             | 45.8 (1330/2906)                         | 5.20 (1330/256)                            |
|                | HPV+       | Cytoplogy   | 59.0 (77/4,859)     | 57.8 (75/83.9)      | 65.7 (56/70.5) | 60.5 (57.4/61.2) | 18.1 (21/20.3)          | 23.5 (21.1/23.5)                            | 2.8 (2.8)                                 | 4.4 (3.8)                                 | 44.0 (128/1854)                           | 4.93 (1052/184)                           |

Notes: Sensitivity and Specificity are calculated at baseline and cumulative per disease status. PPV and 1-NPV are calculated at baseline and cumulative per disease status.
| Disease status | HPV Status | Triage with | Sensitivity % (n/N) | Specificity % (n/N) | PPV % (n/N) | 1-NPV % (n/N) | Positivity rate % (n/N) | Number of baseline colpos per disease detected % (n/N) |
|----------------|------------|------------|---------------------|---------------------|-------------|---------------|------------------------|----------------------------------|
| ≥CIN3          | HPV16/18+  | DS         | Baseline            | Cumulative          | Baseline    | Cumulative    | Baseline              | Cumulative                      | Baseline |
|                |            |            | 93.2 (123/132)     | 92.7 (139/150)     | 42.5 (291/685) | 43.5 (293/674) | 23.8 (123/517)       | 26.7 (139/520)                  | 3.0 (9/300)  |
|                |            |            | (87.5, 96.4)       | (87.3, 95.9)       | (38.8, 46.2) | (39.8, 47.2) | (22.3, 25.2)         | (25.1, 28.3)                    | 3.6 (11/304) |
|                |            |            | Cytology            |                     |             |               |                       |                                  | 4.20 (517/123) |
|                |            |            | 78.8 (104/132)     | 77.3 (116/150)     | 56.6 (388/685) | 57.3 (386/674) | 25.9 (104/401)       | 28.7 (116/404)                  | 6.7 (28/416) |
|                |            |            | (71.1, 84.9)       | (70.0, 83.3)       | (52.9, 60.3) | (53.5, 61.0) | (23.5, 28.3)         | (26.1, 31.2)                    | 8.1 (34/420) |
|                | HPV16+     | DS         | Baseline            | Cumulative          | Baseline    | Cumulative    | Baseline              | Cumulative                      | Baseline |
|                |            |            | 94.0 (110/117)     | 93.8 (120/128)     | 39.2 (187/477) | 40.3 (190/472) | 27.5 (110/400)       | 29.9 (120/402)                  | 3.6 (7/194)  |
|                |            |            | (88.2, 97.1)       | (88.2, 96.8)       | (34.9, 43.7) | (35.9, 44.7) | (25.7, 29.2)         | (28.0, 31.7)                    | (8/198) (400/594) |
|                |            |            | Cytology            |                     |             |               |                       |                                  | 6.73 (637/110) |
|                |            |            | 78.6 (92/117)      | 77.3 (99/128)      | 55.1 (263/477) | 55.7 (263/472) | 30.1 (92/306)        | 32.1 (99/308)                   | 4.0 (25/288) |
|                |            |            | (70.4, 85.1)       | (69.4, 83.7)       | (50.6, 59.5) | (51.2, 60.1) | (27.1, 32.9)         | (29.1, 35.1)                    | 9.9 (29/292) |
|                | HPV18+     | DS         | Baseline            | Cumulative          | Baseline    | Cumulative    | Baseline              | Cumulative                      | Baseline |
|                |            |            | 86.7 (62.1, 96.3)  | 86.4 (66.7, 95.3)  | 50.0 (104/208) | 51.0 (103/202) | 11.1 (13/117)        | 16.1 (19/118)                   | 2.8 (2/106)  |
|                |            |            | (13/15)            | (19/22)            | (103/202) | (103/202) | (13/117)            | (19/118)                        | (3/106) (117/223) |
|                |            |            | Cytology            |                     |             |               |                       |                                  | (117/13) (117/13) |
|                |            |            | 80.0 (54.8, 93.0)  | 77.3 (56.6, 89.9)  | 60.1 (400/110) | 60.9 (123/208) | 12.6 (123/202)       | 17.7 (129/196)                  | 7.9 (3/128)  |
|                |            |            | (12/15)            | (17/22)            | (123/202) | (123/202) | (129/196)           | (17/96)                         | (5/128) (95/225) |
|                | 12 Other HPV+ | DS      | Baseline            | Cumulative          | Baseline    | Cumulative    | Baseline              | Cumulative                      | Baseline |
|                |            |            | 86.2 (81/99)       | 86.8 (1563/2812)   | 55.6 (1581/2827) | 55.9 (81/1330) | 6.1 (99/1345)       | 7.4 (13/1576)                   | 0.8 (3/1356) |
|                |            |            | (77.8, 91.7)       | (79.4, 91.9)       | (53.7, 57.4) | (54.1, 57.7) | (5.5, 6.5)           | (6.7, 7.9)                      | (0.5, 1.3) (44/0.7) |
|                |            |            | Cytology            |                     |             |               |                       |                                  | (0.6, 1.5) (15/1596) |
|                |            |            | 67.0 (77.8, 91.7)  | 65.8 (1823/2812)   | 64.8 (1837/2827) | 65.0 (63/1052) | 6.0 (75/1065)        | 7.0 (63/1052)                   | 1.7 (31/1854) |
|                |            |            | (63/114)           | (75/114)           | (1832/2812) | (1837/2827) | (63/1052)            | (75/1065)                        | (39/1876) (1052/2906) |
|                |            |            | (57.0, 75.7)       | (56.7, 73.9)       | (63.0, 66.6) | (63.2, 66.7) | (5.1, 6.8)           | (6.1, 7.9)                      | (1.2, 2.2) (34.5, 37.9) |

CI, confidence intervals; CIN, cervical intraepithelial neoplasia; DS, Dual-stain; PPV, positive predictive value; NPV, negative predictive value
Supplementary Table 6. Triage performance of Dual-stain and cytology, alone or in combination with HPV16/18 genotyping for detecting ≥CIN2 and ≥CIN3 in cobas 4800 HPV-positive women: baseline and cumulative 1-year data

| Disease status  | Sensitivity % (n/N) 95%CI | Specificity % (n/N) 95%CI | PPV % (n/N) 95%CI | 1-NPV % (n/N) 95%CI | Positivity rate % (n/N) 95%CI | Number of baseline colpos per disease detected |
|-----------------|---------------------------|---------------------------|-------------------|---------------------|-----------------------------|----------------------------------|
| ≥CIN2           |                           |                           |                   |                     |                             |                                  |
| DS              |                           |                           |                   |                     |                             |                                  |
| Cytology        |                           |                           |                   |                     |                             |                                  |
| HPV16/18 GT     |                           |                           |                   |                     |                             |                                  |
| + DS            |                           |                           |                   |                     |                             |                                  |
| ≥CIN3           |                           |                           |                   |                     |                             |                                  |
| DS              |                           |                           |                   |                     |                             |                                  |
| Cytology        |                           |                           |                   |                     |                             |                                  |
| HPV16/18 GT     |                           |                           |                   |                     |                             |                                  |
| + DS            |                           |                           |                   |                     |                             |                                  |

CI, confidence intervals; CIN, cervical intraepithelial neoplasia; DS, Dual-stain; GT, genotypes; PPV, positive predictive value; NPV, negative predictive value
Supplementary Figure 1. Flow of subjects through baseline and follow-up phases of the IMPACT trial.
Note: There were 480 (DS positive), 495 (DS negative), and 78 (DS unsatisfactory) cases with no baseline CPR results, which made them eligible to be referred to the 1-year follow-up phase. Among them, there were 18, 24, and 7 cases in the DS positive, DS negative, and DS unsatisfactory categories, respectively, which had valid 1-year CPR results. CPR, central pathology review; NILM, negative for intraepithelial lesion or malignancy; CIN, cervical intraepithelial neoplasia; ACIS, adenocarcinoma in-situ
**Supplementary Figure 3.** Risk of ≥CIN3 in cobas 4800 HPV-positive women dependent on HPV genotype group, cytology, and Dual-stain results.

Cumulative 1-year risks of ≥CIN3 for HPV genotype groups (16/18+, 12 Other+), cytology (NILM; ≥ASC-US), and Dual-stain (DS+; DS-) test results are plotted on the y-axis, with the number of subjects within the respective categories indicated.