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Cervical histology after routine ThinPrep or SurePath liquid-based cytology and computer-assisted reading in Denmark

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Background: We compared the sensitivity and specificity of liquid-based cytology (LBC) and computer-assisted reading for SurePath/FocalPoint and ThinPrep with those of manually read conventional cytology in routine cervical screening in four Danish laboratories.

Methods: Using data from five nationwide registers, technological phases were identified by slide preparation, reading technique, and triage of borderline cytology. Trends in the detection of cervical intraepithelial neoplasia (CIN) were an indicator of the technology's relative sensitivity, and trends in false-positive tests an indicator of relative specificity.

Results: At 23–29 years, SurePath/FocalPoint statistically significantly increased the detection of $\geqslant$CIN3 by 85% compared with manually read conventional cytology. The 11% increase with ThinPrep was not significant. At 30–44 years, the increase with SurePath/FocalPoint was 58%; the 16% increase with ThinPrep was not significant. At 45–59 years, both technologies led to nonsignificant decreases in the detection. SurePath/FocalPoint doubled the frequency of false-positive tests at any age. With ThinPrep, these proportions remained the same at 23–29 years, but decreased by two-thirds at 45–59 years. In a fourth laboratory with continuous use of manually read conventional cytology, no such trends were seen.

Conclusions: The sensitivity and specificity of modern LBC and computer-assisted reading technologies may be brand- and age-dependent.

In the past two decades, the classical Pap smear has been replaced by liquid-based cytology (LBC), whereas manual reading is now assisted by computer reading. At present, the cytology market is dominated by ThinPrep (Hologic, Bedford, MA, USA) and SurePath/FocalPoint (BD, Franklin Lakes, NJ, USA) technologies. The advantages of LBC include purified stains, cell monolayers, and the ability to run additional analyses on the same sample, for example, for human papillomavirus (HPV) or biomarker expression testing. Computer-assisted reading systems deselect normal samples and point cytologists to the most critical areas in suspect samples.

The use of the new technologies has also affected women. In two routine Danish laboratories, the switch to SurePath LBC significantly increased the proportions of abnormal cytological samples at age <45 years, and decreased them in older women (Barken *et al*, 2014; Rask *et al*, 2014). ThinPrep LBC in another

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Danish laboratory was associated with a decreased proportion of abnormal cytological samples at any age. This decrease was especially large around menopause, possibly because LBC makes neoplastic lesions more easily distinguished from, for example, atrophy. Computer-assisted reading technologies increased the proportions of abnormal cytology regardless of the brand and the woman's age.

These changes led to a different selection of women referred for further follow-up. The next question is, therefore, whether there was also a change in the detection of high-grade cervical intraepithelial neoplasia (CIN). Previous trials comparing LBC and/or computer-assisted reading to conventional methods led to conflicting results regarding the changed CIN detection; some suggested a statistically significantly decreased, some equal, and some a significantly increased detection (Arbyn *et al*, 2008; Kitchener *et al*, 2011a; Klug *et al*, 2013).

Based on routine screening data from four laboratories evaluating about one-third of all cytology in Denmark, we aimed to determine whether the age-specific changes in abnormal cytology described above led to changes in the detection of histologically confirmed high-grade CIN.

MATERIALS AND METHODS

Cervical screening has been undertaken in Denmark since the 1960s. In 1986, organised cytological screening at age 23–59 years was recommended every 3 years. Since 2007, women aged 50–65 years have been targeted every 5 years, whereas since 2012, women aged $\geqslant 60$ years can be 'checked out' of the programme following a negative HPV test result. Screening coverage has been around 75%, with negligible regional variation.

Previously, we studied changes in the detection of atypical squamous cells of undetermined significance or worse ($\geqslant$ ASCUS) following the introduction of LBC and computer-assisted reading technologies in 1998–2007 in Departments of Pathology of Copenhagen University Hospital Hvidovre, Hillerød Hospital, and Odense University Hospital (Table 1) (Barken *et al*, 2013; Rask *et al*, 2014). Department of Pathology of Roskilde County Hospital, retaining manually read conventional cytology, was used to study technology-independent changes, for example, changes in the background risk of cervical cancer. Each laboratory served well-defined catchment areas: Hvidovre laboratory received samples from Copenhagen and Frederiksberg Municipalities; Hillerød from Frederiksborg County; Roskilde from Roskilde County; and Odense from Funen County. The coverage rates of the target population were stable, as was the case-mix of samples (screening *vs* follow-up).

Data sources. We retrieved the information on the women's age and place of residence from the Danish Civil Registration System. Since 1968, every resident has been registered with a unique identification number (CPR number). Data on cervical cytology and biopsies including their diagnoses were obtained from the Pathology Data Bank (Patobank). We also retrieved data on conisations from the Patobank; since mid-1990s, conisations were most frequently undertaken as large loop excisions of the transformation zone and had a specific Danish Systematised Nomenclature of Medicine (SNOMED) code. Additional data on cervical treatments including conisations, destructive therapies, hysterectomies, excisions, and other less frequent types of treatment (Barken *et al*, 2012) were retrieved from (a) the National Patient Register where information on in-patient treatments and the associated diagnoses has been available since 1978, and on out-patient treatments since 1995, and from (b) the National Health Service Register containing non-diagnostic information on biopsies and cervical treatments undertaken by private gynaecologists since

1990. The Danish Cancer Register was used to obtain information on incident cervical cancers since 1943. Data were retrieved from the beginning of the registration until end of 2010 and were linked using the CPR number.

In the Patobank, diagnoses were registered using the SNOMED classification. Diagnoses were classified into Bethesda 2001 categories. An exception was made for Hvidovre (Barken *et al*, 2014), where samples from women aged $\geqslant 30$ years with an initial ASCUS diagnosis and a negative reflex HPV test were, during a limited time period, routinely downgraded to normal cytology. As these women were recommended for repeated testing despite the nominally normal diagnosis, we reclassified them as having ASCUS.

Technology phases. Laboratories were autonomous in making decisions regarding the technology and the combinations of slide preparation and reading technologies differed even between the laboratories that used the same brand. Consequently, data were analysed for each laboratory separately.

As described previously (Barken *et al*, 2013; Rask *et al*, 2014), technological phases were identified by slide preparation, reading technique, and triage of ASCUS at $\geqslant 30$ years. All piloting and implementation periods were excluded. 'Baseline' in phase 1 was defined for all laboratories as manual reading of conventional cytology with cytological triage of ASCUS. The Odense laboratory returned to manually read conventional cytology after a ThinPrep LBC pilot. Because the differences in the proportions of all studied end points were not statistically significant, data for pre- and postpilot periods were merged (excluding the pilot).

In phase 2, Hvidovre laboratory started using FocalPoint reading technology. FocalPoint Slide Profiler replaced manual reading, and the cutoff for no further review of normal samples was set to 50% following an internal pilot. The remaining samples were automatically divided into five quintiles of likelihood of abnormalities. In phase 3, SurePath LBC replaced conventional cytology, whereas the laboratory continued using FocalPoint Slide Profiler with a 50% cutoff. This cutoff was changed to the manufacturer's recommended 25% in phase 4, meaning that cytotechnicians and pathologists had to evaluate 75% instead of 50% of all samples. Additionally, cytology was replaced by HPV testing in triage of ASCUS at age $\geqslant 30$ years using Qiagen's Hybrid Capture 2 (HC2) assay. In phase 5, FocalPoint GS Imaging System was added, which, in the 75% of samples not automatically signed out by the FocalPoint Slide Profiler, guided the cytotechnicians through 16 preselected fields of view (most likely to contain abnormalities).

Hillerød laboratory closely followed the changes made in Hvidovre. In phase 2, it introduced FocalPoint Slide Profiler with the 50% cutoff, which was changed to 25% in phase 3 together with introducing SurePath LBC. In phase 4, FocalPoint GS Imaging System was added. Throughout the study period, ASCUS was triaged with cytology.

Odense laboratory started using ThinPrep technology in phase 2 when conventional cytology was replaced by LBC using ThinPrep Pap test in T3000 processor (Hologic). In phase 3, ThinPrep Imaging System (Hologic) including Imaging Pap Stain replaced conventional Pap stain and manual reading. The system guided the cytotechnician to 22 fields of view. Also here, cytology was used to triage ASCUS in all phases.

To determine potential trends in Roskilde, manually read conventional cytology data were analysed in arbitrary 3-year periods.

Inclusion criteria. We included samples taken from 1 January 1998 to 31 December 2007 at age 23–59 years, the target age until 2007. As an exception, we excluded year 2007 for Hillerød and Roskilde since a national administrative reorganisation led to changes in their catchment areas. Samples taken for follow-up of

Table 1. Description of phases by laboratory				
Laboratory (county catchment area) and phase	Period	Slide preparation	Reading technique	Triage
Roskilde (Roskilde County)				
Phase 1	1 January 1998 to 31 December 2000	Conventional cytology	Manual	Cytology
Phase 2	1 January 2001 to 31 December 2003	As above	As above	As above
Phase 3	1 January 2004 to 31 December 2006	As above	As above	As above
Hvidovre (Copenhagen and Frederiksberg Municipalities)[a]				
Phase 1	1 January 1998 to 30 September 1999	Conventional cytology	Manual	Cytology
Phase 2	1 July 2000 to 30 April 2002	As above	Computer-assisted (BD FocalPoint Slide Profiler, 50% cutoff)	As above
Phase 3	1 August 2002 to 30 April 2005	LBC (SurePath Pap test, BD PrepStain Slide Processor)	As above	As above
Phase 4	1 October 2005 to 30 November 2006	As above	Computer-assisted (BD FocalPoint Slide Profiler, 25% cutoff)	HPV DNA (Qiagen Hybrid Capture 2)[b]
Phase 5	1 April 2007 to 31 December 2007	As above	Computer-assisted (as above plus BD FocalPoint GS Imaging System)	As above
Hillerød (Frederiksborg County)[c]				
Phase 1	1 January 1998 to 31 July 2002	Conventional cytology	Manual	Cytology
Phase 2	1 September 2002 to 31 December 2003	As above	Computer-assisted (BD FocalPoint Slide Profiler, 50% cutoff)	As above
Phase 3	1 October 2004 to 31 October 2005	LBC (BD SurePath Pap test, BD PrepStain Slide processor)	Computer-assisted (BD FocalPoint Slide Profiler, 25% cutoff)	As above
Phase 4	1 February 2006 to 31 October 2006	As above	Computer-assisted (as above plus BD FocalPoint GS Imaging System)	As above
Odense (Funen County)				
Phase 1a	1 January 1998 to 31 December 1998	Conventional cytology	Manual	Cytology
Phase 1b	1 November 1999 to 31 May 2001	As above	As above	As above
Phase 2	1 January 2004 to 30 September 2004	LBC (Hologic ThinPrep Pap test, T3000 Slide Processor)	As above	As above
Phase 3	1 October 2006 to 31 December 2007	As above	Computer-assisted (Hologic ThinPrep Imaging System)	As above

Abbreviations: ASCUS = atypical squamous cells of undetermined significance; HPV = human papillomavirus; LBC = liquid-based cytology. *Note*: All periods between phases represented periods of piloting and implementation of the technology, and were excluded from the study.

[a]Owing to incomplete histological registration before 2001 for women residing in Frederiksberg Municipality, data were analysed separately by municipality (from phase 1 onwards for women residing in Copenhagen Municipality, and for Frederiksberg Municipality only from phase 2 onwards).

[b]This also signifies a change in the recommended follow-up. Whereas with cytological triage, all women with ASCUS were recommended for repeated testing at 6/12 months, they were recommended for immediate colposcopy if HPV-positive, and for repeated testing in 12 months if HPV-negative.

[c]Owing to incomplete histological registration for women residing in Frederiksborg County, only data for samples taken from 1 January 2003 onwards were included in the analysis, that is, from phase 2 onwards.

recent abnormalities were excluded. Previous analyses (Barken *et al*, 2013; Rask *et al*, 2014) used the same definitions.

The worst histological outcome was determined within 2.5 years after the abnormal cytological sample. Women who died or emigrated from Denmark during the follow-up were excluded. Some biopsies were evaluated by private pathologists who were historically not obliged to report their diagnostic data to the Patobank. Women were, therefore, also excluded if they lived in, or moved to, a county with inadequate histological registration in the Patobank, defined as registration of <85% of all biopsies (Barken *et al*, 2012). This implies exclusion of samples from Hillerød before 1 January 2003, and from Hvidovre/Frederiksberg before 1 January 2001.

Samples taken for follow-up of recent abnormalities were those with a preceding cervical cancer diagnosis; CIN diagnosis or treatment in ≤10 years; high-grade cervical squamous intraepithelial lesions or worse (≥HSIL), inadequate cytology, or a positive HPV test result in the past 12 months; and inadequate/negative histology, low-grade cervical intraepithelial lesions, or ASCUS in the past 15 months. The remaining were predominantly screening samples, taken either in organised or opportunistic settings. As the indication for sample taking was not registered, they may have also contained a small proportion of samples taken for investigation of symptoms. The proportion of the latter samples was assumed not to be associated with the technological phases.

Statistical analysis. ASCUS was the cutoff for abnormal cytology as it was the indication for further follow-up. The following end points were determined per 100 screening samples: detection of histologically confirmed CIN2 and ≥CIN3, number of CIN treatments (all indicators of cytology's sensitivity), detection of histologically confirmed <CIN2, and number of false-positive samples (indicators of specificity). False-positive samples were defined as ≥ASCUS without ≥CIN2 or ≥CIN3 during follow-up (Rebolj *et al*, 2012). Cervical intraepithelial neoplasia treatments included all conisations (most frequently undertaken as large-loop excision of the transformation zone), and destructive therapies, hysterectomies, excisions, and other less frequent treatments if histological CIN of any grade was registered in the period between

3 months before and 1 month after the treatment (Barken *et al*, 2012). We calculated the positive predictive value (PPV) for ≥CIN2 and ≥CIN3 as the number of detected lesions per 100 screening samples with an ≥ASCUS diagnosis.

The main comparison was between manually read conventional cytology (baseline/phase 1) and full implementation of modern cytological technologies by end of 2007 (the last phase per laboratory). Per laboratory, we calculated relative proportions (RPs) of the observed end points in the final phase compared with the baseline. The data for the baseline situation were not available for Hvidovre/Frederiksberg and Hillerød, thus these laboratories did not contribute here. To assess the contribution of each change in technology, we also calculated RP comparing with the previous phase. We stratified the comparisons by age group (23–29, 30–44, and 45–59 years). The 95% confidence intervals (CI) for RP were calculated assuming log-normal distribution.

Proportions of ≥ASCUS were a focus of previous publications (Barken *et al*, 2014; Rask *et al*, 2014), and were not further discussed here. Because for the present analysis the definition of the at-risk population excluded women whose histological outcomes could not be reliably determined, these proportions were tabulated anew. The proportions of women with ≥ASCUS with and without the exclusion were similar.

RESULTS

Study population. In total, 674 248 samples were included: 151 135 from Roskilde, 283 310 from Hvidovre/Copenhagen, 38 831 from Hvidovre/Frederiksberg, 71 915 from Hillerød, and 129 057 from Odense (Table 2). Relatively few samples from counties with incomplete histological registration were excluded (Table A1), most often from Hvidovre serving the area with traditionally highest rates of migration to other counties. The age distribution and completeness of routine follow-up did not change substantially between phases in each laboratory. Most abnormal samples (≥90%) had follow-up. The Roskilde, Odense, and Hillerød laboratories served a population with a higher average age than Hvidovre (Table A2).

Changes in the laboratory with continuous use of manually read conventional cytology. In Roskilde, few changes between the last and the first phase were observed (Table 3 and Figure 1: detection of ≥CIN2; Figure 2: detection of <CIN2; and Figure 3: false-positive tests). The changes were only significant for the proportions of false-positive tests and <CIN2 biopsies, particularly at 45–59 years. A more detailed phase-by-phase comparison by age revealed some fluctuations but no trends (Table A3).

Changes with SurePath technologies. In Hvidovre/Copenhagen, full implementation of SurePath/FocalPoint LBC and reading technologies compared with manually read conventional cytology was associated with a doubling of the frequency of all studied outcomes at 23–44 years, with the exception of a decreased PPV for ≥CIN2/≥CIN3. In older women, 45–59 years, the only statistically significant change was a doubling of the frequency of false-positive tests, and a corresponding decrease in the PPV.

The first step toward computer-assisted reading using a 50% cutoff on FocalPoint Slide Profiler (comparing phase 2 with phase 1, using conventional cytology and cytological triage of ASCUS in both phases) had little impact on the studied outcomes (Table A4). At 23–29 years, however, the frequency of <CIN2 biopsies and false-positive tests increased significantly by 10–30%. At 45–59 years, detection of ≥CIN3 statistically significantly decreased (by 36%). The overall PPV for ≥CIN2/≥CIN3 decreased by 13%.

SurePath LBC implementation (comparing phase 3 with phase 2, using FocalPoint Slide Profiler for reading with a 50% cutoff and cytological triage of ASCUS in both phases) was associated with a statistically significantly increased detection of <CIN2, high-grade CIN, and the frequency of CIN treatments at 23–29 years, all by 30–40%, and in the frequency of false-positive tests by >50%. The increases were slightly smaller at 30–44 years. In women around menopause, 45–59 years, the decreases in CIN detection and in false-positive tests after the introduction of LBC were generally not statistically significant.

After a change in the FocalPoint Slide Profiler's cutoff from 50 to 25%, and a concurrent introduction of HPV triage for ASCUS (comparing phase 4 to phase 3 using SurePath LBC in both phases), statistically significant increases in all studied outcomes were observed at 23–44 years (by ∼ +20–30%). At 45–59 years, significantly increased frequency was observed for <CIN2 biopsies (+23%), ≥CIN3 (+66%), and false-positive tests (+73%).

The addition of FocalPoint GS Imaging System (comparing phase 5 with phase 4, using FocalPoint Slide Profiler with a 25% cutoff, SurePath LBC, and HC2 triage of ASCUS in both phases) was associated with statistically insignificant increases in the frequency of most studied outcomes. However, at 30–59 years, the frequency of false-positive tests increased significantly (by ∼ +20%), and so did the frequency of <CIN2 biopsies at 23–44 years (+25–30%).

Similar patterns in the RP of the studied outcomes across phases were seen also at Hvidovre/Frederiksberg (Table A5) and Hillerød (Table A6).

Changes with ThinPrep technologies. After full implementation of ThinPrep LBC and reading technologies in Odense, the detection of CIN2 and the frequency of CIN treatments statistically significantly increased at 23–29 years, by 77 and 22%, respectively. Among older women, the decreases in the frequency of <CIN2 biopsies (−29% at 30–44 years and −61% at 45–59 years) and of false-positive tests (−36% at 30–44 years and −65% at 45–59 years) were statistically significant (Table 3). Correspondingly, the overall PPV increased by 51% (for ≥CIN2) and 41% (for ≥CIN3); at age 45–59 years, the increase was particularly high, 105% for ≥CIN2.

ThinPrep LBC implementation (comparing phase 2 with phase 1, using manual reading in both phases) was associated with a statistically significant decrease in the frequency of false-positive tests at all ages (−18% at 23–29 years, −53% at 30–44 years, and −76% at 45–59 years; Table A7). The frequency of <CIN2 biopsies also decreased (−41% at 30–44 years and −69% at 45–59 years). There was a tendency toward a decreased detection of CIN2 and a slightly increased detection of ≥CIN3 in all three age groups, although these changes were not statistically significant. The PPV increased particularly at 30–44 years (by 83% for ≥CIN3) and at 45–59 years (by 302% for ≥CIN3).

With ThinPrep Imaging System (comparing phase 3 with phase 2, using ThinPrep LBC in both phases), the detection of CIN2 at 23–29 years increased significantly (+135%), and detection of ≥CIN3 at 45–59 years decreased (−53%). Also, the frequency of false-positive tests increased, by 34% at 30–44 years, and by 45% at 45–59 years. Consequently, the PPV decreased, by 24% (for ≥CIN3) at 23–29 years, and by 63% (for ≥CIN3) at 45–59 years.

DISCUSSION

General findings. In the Danish routine screening data, cytology using SurePath LBC and FocalPoint computer-assisted reading technologies (with possibly also an intervening effect of HPV triage) appeared to be more sensitive for the detection of high-grade CIN but less specific compared with manually read conventional cytology, predominantly at younger ages. ThinPrep LBC, on the other hand, decreased the sensitivity toward CIN2, but

Table 2. Primary cytology samples and histological outcomes after 2.5-year follow-up[a]					
	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5
Unchanged technology: Roskilde	Baseline: Conventional cytology, manual reading, cytology triage of ASCUS (N = 53 979)	Conventional cytology, manual reading, cytology triage of ASCUS (N = 49 856)	Conventional cytology, manual reading, cytology triage of ASCUS (N = 47 300)	Not relevant	Not relevant
⩾ASCUS	1173 (2%)	**1251 (3%)**	**1012 (2%)**	—	—
CIN2	118 (0.22%)	104 (0.21%)	85 (0.18%)	—	—
⩾CIN3	281 (0.52%)	289 (0.58%)	271 (0.57%)	—	—
CIN treatments	482 (0.9%)	491 (1.0%)	**405 (0.9%)**	—	—
<CIN2	471 (0.87%)	439 (0.88%)	323 (0.68%)	—	—
False positive for ⩾CIN2	774 (1.4%)	**858 (1.7%)**	656 (1.4%)	—	—
False positive for ⩾CIN3	892 (1.7%)	**962 (1.9%)**	741 (1.6%)	—	—
PPV for ⩾CIN2	34%	31%	35%	—	—
PPV for ⩾CIN3	24%	23%	**27%**	—	—
SurePath technology: Hvidovre (Copenhagen)	Baseline: Conventional cytology, manual reading, cytology triage of ASCUS (N = 62 644)	Conventional cytology, FocalPoint Slide Profiler 50% cutoff, cytology triage of ASCUS (N = 59 274)	SurePath LBC, FocalPoint Slide Profiler 50% cutoff, cytology triage of ASCUS (N = 94 541)	SurePath LBC, FocalPoint Slide Profiler 25% cutoff, HC2 triage of ASCUS (N = 43 002)	SurePath LBC, FocalPoint Slide Profiler 25% cutoff + FocalPoint Imaging System, HC2 triage of ASCUS (N = 23 849)
⩾ASCUS	2299 (4%)	2307 (4%)	**4832 (5%)**	**2751 (6%)**	**1742 (7%)**
CIN2	230 (0.37%)	201 (0.34%)	**423 (0.45%)**	**242 (0.56%)**	162 (0.68%)
⩾CIN3	624 (1.00%)	547 (0.92%)	**1148 (1.21%)**	**641 (1.49%)**	394 (1.65%)
CIN treatments	857 (1.4%)	828 (1.4%)	**1780 (1.9%)**	**959 (2.2%)**	**603 (2.5%)**
<CIN2	722 (1.15%)	**801 (1.35%)**	**1414 (1.50%)**	**844 (1.96%)**	**581 (2.44%)**
False positive for ⩾CIN2	1445 (2.3%)	**1559 (2.6%)**	**3261 (3.4%)**	**1868 (4.3%)**	**1186 (5.0%)**
False positive for ⩾CIN3	1675 (2.7%)	**1760 (3.0%)**	**3684 (3.9%)**	**2110 (4.9%)**	**1348 (5.7%)**
PPV for ⩾CIN2	37%	**32%**	33%	32%	32%
PPV for ⩾CIN3	27%	**24%**	24%	23%	23%
SurePath technology: Hvidovre (Frederiksberg)	Baseline: As above (excluded)	As above (N = 9385)	As above (N = 17 634)	As above (N = 7018)	As above (N = 4794)
⩾ASCUS	—	361 (4%)	**830 (5%)**	**420 (6%)**	**352 (7%)**
CIN2	—	26 (0.28%)	**77 (0.44%)**	**51 (0.73%)**	39 (0.81%)
⩾CIN3	—	97 (1.03%)	195 (1.11%)	**107 (1.52%)**	80 (1.67%)
CIN treatments	—	134 (1.4%)	304 (1.7%)	**169 (2.4%)**	140 (2.9%)
<CIN2	—	113 (1.20%)	239 (1.36%)	105 (1.50%)	**122 (2.54%)**
False positive for ⩾CIN2	—	238 (2.5%)	**558 (3.2%)**	262 (3.7%)	233 (4.9%)
False positive for ⩾CIN3	—	264 (2.8%)	**635 (3.6%)**	313 (4.5%)	272 (5.7%)
PPV for ⩾CIN2	—	34%	33%	38%	34%
PPV for ⩾CIN3	—	27%	23%	25%	23%
SurePath technology: Hillerød	Baseline: Conventional cytology, manual reading, cytology triage of ASCUS (excluded)	Conventional cytology, FocalPoint Slide Profiler 50% cutoff, cytology triage of ASCUS (N = 28 888)	SurePath LBC, FocalPoint Slide Profiler 25% cutoff, cytology triage of ASCUS (N = 24 593)	SurePath LBC, FocalPoint Slide Profiler 25% cutoff + FocalPoint Imaging System, cytology triage of ASCUS (N = 18 434)	Not relevant
⩾ASCUS	—	878 (3%)	**865 (4%)**	843 (5%)	—
CIN2	—	67 (0.23%)	71 (0.29%)	**77 (0.42%)**	—
⩾CIN3	—	151 (0.52%)	**183 (0.74%)**	181 (0.98%)	—
CIN treatments	—	281 (1.0%)	**291 (1.2%)**	280 (1.5%)	—
<CIN2	—	318 (1.10%)	298 (1.21%)	**275 (1.49%)**	—
False positive for ⩾CIN2	—	660 (2.3%)	611 (2.5%)	**585 (3.2%)**	—
False positive for ⩾CIN3	—	727 (2.5%)	682 (2.8%)	**662 (3.6%)**	—
PPV for ⩾CIN2	—	25%	**29%**	31%	—
PPV for ⩾CIN3	—	17%	**21%**	21%	—

Table 2. (Continued)					
	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5
ThinPrep technologies: Odense	Baseline: Conventional cytology, manual reading, cytology triage of ASCUS ($N=74\,522$)	ThinPrep LBC, manual reading, cytology triage of ASCUS ($N=20\,921$)	ThinPrep LBC, ThinPrep Imaging System, cytology triage of ASCUS ($N=33\,614$)	Not relevant	Not relevant
⩾ASCUS	3423 (5%)	**536 (3%)**	**1087 (3%)**	—	—
CIN2	183 (0.25%)	**31 (0.15%)**	**106 (0.32%)**	—	—
⩾CIN3	557 (0.75%)	163 (0.78%)	249 (0.74%)	—	—
CIN treatments	826 (1.1%)	219 (1.0%)	389 (1.2%)	—	—
<CIN2	1507 (2.02%)	**215 (1.03%)**	**433 (1.29%)**	—	—
False positive for ⩾CIN2	1683 (3.6%)	**342 (1.6%)**	**732 (2.2%)**	—	—
False positive for ⩾CIN3	2866 (3.8%)	**373 (1.8%)**	**838 (2.5%)**	—	—
PPV for ⩾CIN2	22%	**36%**	33%	—	—
PPV for ⩾CIN3	16%	**30%**	**23%**	—	—

Abbreviations: ASCUS = atypical squamous cells of undetermined significance; CI = confidence interval; CIN = cervical intraepithelial neoplasia; HC2 = Hybrid Capture 2; LBC = liquid-based cytology; PPV = positive predictive value; RP = relative proportion; triage = in case of ASCUS at age ⩾30 years. Bold signifies significant change comparing the current phase with the most recent preceding phase, based on 95% CI for the calculated RP.
[a]In women aged 23–59 years, by laboratory and phase.

with higher specificity compared with conventional cytology, particularly at older ages. ThinPrep computer-assisted reading technologies were associated with a decrease in the specificity compared with manual reading, but generally without corresponding increases in high-grade CIN detection other than of CIN2 in young women.

Comparison with the literature. In particular, the early literature on new cytological technologies was dominated by studies in the so-called 'referral populations'. These women represented selected subgroups of the screening population (Rebolj *et al*, 2014a), identified as eligible after presenting with abnormal conventional cytology. Hence, unlike in our study, lesions detectable using LBC but less likely to be seen on conventional cytology would not be considered. This might be one of the reasons why an influential meta-analysis from 2008 concluded that LBC is as sensitive for detection of ⩾CIN2 as conventional cytology, relative sensitivity 1.03 (95% CI: 0.97–1.09) (Arbyn *et al*, 2008).

The LBC literature on primary screening has been dominated by ThinPrep studies, but those led to widely differing results. In a small French screening study ($n=1757$), in which all women underwent colposcopy, the sensitivity of ThinPrep LBC was 66% (95% CI: 56–75), slightly but significantly ($P<0.05$) lower compared with that of conventional cytology, 72% (95% CI: 63–80) (Coste *et al*, 2003). In that study, LBC slides were made from the material remaining after the conventional slides had been prepared. Consistent with our data, two large randomised controlled trials, from the Netherlands ($n=89\,784$) and Italy ($n=45\,174$), observed the same detection of high-grade CIN with ThinPrep LBC and conventional cytology (Ronco *et al*, 2007; Siebers *et al*, 2009). However, in a smaller Swedish trial ($n=13\,484$) ThinPrep LBC detected 62% (95% CI: 22–116) more high-grade CIN compared with conventional cytology (Strander *et al*, 2007). Also in a German trial comparing ThinPrep LBC with conventional cytology at ⩾20 years ($n=20\,935$) (Klug *et al*, 2013), ThinPrep LBC detected substantially more ⩾CIN2 compared with conventional cytology, RR: 2.40 (95% CI: 1.49–3.87). Although other factors probably also had a role, the sensitivity of conventional cytology might have differed across these studies. Reading of conventional cytology tended to rely on internal training, potentially allowing for interlaboratory variation. For patented LBC technologies, the training and certification is the manufacturer's responsibility, and the clinical outcomes thereof might be more uniform across laboratories.

A dearth of SurePath LBC studies with histological confirmation of CIN created a void in the literature, thus our findings of an increased sensitivity at younger ages could not be adequately compared. There are three major differences between ThinPrep and SurePath LBC that may have contributed to the observed variation in CIN detection. First, ThinPrep contains methanol, whereas SurePath contains formaldehyde and ethanol, leading to a different morphology presentation on the final microscopy slide. Second, SurePath cell material is first cleaned up for mucus and debris on a column. ThinPrep is processed directly out of the vial; samples are aspirated through a filter and dispensed onto the slide, which potentially leaves cell material in the filter. Finally, for a ThinPrep sample, the brush is rinsed in the liquid and afterwards discarded by the smear taker, whereas the brush head is left in SurePath until the cell material is transferred to the preprocessing column before sedimentation on the cytology slide in the laboratory. Taken together with the different vial sizes (20 ml for ThinPrep and 10 ml for SurePath), this may potentially yield differences in the available cellularity (Bigras *et al*, 2003; Umana *et al*, 2013).

There have been few large evaluations of computer-assisted reading technology with a histological reference. Most notably, the large UK randomised controlled trial MAVARIC ($n=73\,266$) compared ThinPrep and FocalPoint imaging-assisted reading with manual reading in predominantly primary screening samples (Kitchener *et al*, 2011b). Samples from some non-randomised practices and from colposcopy clinics were included to raise the number of abnormal samples. Unlike in our study, both ThinPrep and FocalPoint were inferior in detecting high-grade CIN; compared with manual reading, the relative sensitivity for ⩾CIN2 was 0.92 (95% CI: 0.87–0.98) for ThinPrep and 0.90 (95% CI: 0.85–0.96) for FocalPoint. In the German trial, the addition of computer-assisted reading to LBC slightly increased the relative detection of ⩾CIN2 compared with manually read conventional cytology, from 2.40 (with ThinPrep LBC alone, see above) to 2.70 (95% CI: 1.69–4.31; for ThinPrep LBC + computer-assisted reading). Also in two large Australian screening laboratories, ThinPrep LBC combined with Imaging missed fewer high-grade CIN compared with manually read conventional cytology (Davey *et al*, 2007; Halford *et al*, 2010).

Table 3. Effect of full implementation of SurePath/FocalPoint or ThinPrep LBC and computer-assisted reading (last phase)[a]

	No change (Roskilde)[b]	SurePath (Hvidovre [CPH M])[c]	ThinPrep (Odense)[d]
Before	Baseline: Conventional cytology, manual reading, cytology triage of ASCUS	Baseline: conventional cytology, manual reading, cytology triage of ASCUS	Baseline: Conventional cytology, manual reading, cytology triage of ASCUS
After	As above	SurePath LBC, FocalPoint Slide Profiler 25% cutoff + FocalPoint Imaging System, HC2 triage of ASCUS	ThinPrep LBC, ThinPrep Imaging System, cytology triage of ASCUS
23–59 years	47 300/53 979	23 849/62 644	33 614/74 522
⩾ASCUS	1012/1173, 0.98 (0.91–1.07)	**1742/2299, 1.99 (1.87–2.11)**	**1087/3423, 0.70 (0.66–0.75)**
CIN2	85/118, 0.82 (0.62–1.09)	**162/230, 1.85 (1.51–2.26)**	**106/183, 1.28 (1.01–1.63)**
⩾CIN3	271/281, 1.10 (0.93–1.30)	**394/624, 1.66 (1.46–1.88)**	249/557, 0.99 (0.85–1.15)
CIN treatments	405/482, 0.96 (0.84–1.09)	**603/857, 1.85 (1.67–2.05)**	389/826, 1.04 (0.93–1.18)
<CIN2	**323/471, 0.78 (0.68–0.90)**	**581/722, 2.11 (1.90–2.36)**	**433/1507; 0.64 (0.57–0.71)**
False positive for ⩾CIN2	656/774, 0.97 (0.87–1.07)	**1186/1445, 2.16 (2.00–2.32)**	**732/2683, 0.60 (0.56–0.66)**
False positive for ⩾CIN3	741/892, 0.95 (0.86–1.04)	**1348/1675, 2.11 (1.97–2.27)**	**838/2866, 0.65 (0.60–0.70)**
PPV for ⩾CIN2	35%/34%, 1.03 (0.92–1.16)	**32%/37%, 0.86 (0.79–0.94)**	**33%/22%, 1.51 (1.36–1.68)**
PPV for ⩾CIN3	27%/24%, 1.12 (0.97–1.29)	**23%/27%, 0.83 (0.75–0.93)**	**23%/16%, 1.41 (1.23–1.61)**
23–29 years	5572/7350	8228/21 536	5310/14 299
⩾ASCUS	215/273, 1.04 (0.87–1.24)	**815/1020, 2.09 (1.91–2.28)**	435/1066, 1.10 (0.99–1.22)
CIN2	22/38, 0.76 (0.45–1.29)	**94/136, 1.81 (1.39–2.35)**	**61/93, 1.77 (1.28–2.44)**
⩾CIN3	71/73, 1.28 (0.93–1.78)	**204/288, 1.85 (1.55–2.21)**	103/250, 1.11 (0.88–1.39)
CIN treatments	103/133, 1.02 (0.79–1.32)	**326/411, 2.08 (1.80–2.40)**	**167/373, 1.21 (1.01–1.44)**
<CIN2	49/91, 0.71 (0.50–1.00)	**258/258, 2.62 (2.21–3.10)**	142/372, 1.03 (0.85–1.24)
False positive for ⩾CIN2	122/162, 0.99 (0.79–1.25)	**517/596, 2.27 (2.02–2.55)**	271/723, 1.01 (0.88–1.16)
False positive for ⩾CIN3	144/200, 0.95 (0.77–1.17)	**611/732, 2.18 (1.97–2.43)**	332/816, 1.10 (0.97–1.24)
PPV for ⩾CIN2	43%/41%, 1.06 (0.86–1.31)	**37%/42%, 0.88 (0.78–0.99)**	**38%/32%, 1.17 (1.01–1.36)**
PPV for ⩾CIN3	33%/27%, 1.23 (0.94–1.62)	25%/28%, 0.89 (0.76–1.03)	24%/23%, 1.01 (0.83–1.23)
30–44 years	21 827/23 376	10 081/24 753	14 370/32 819
⩾ASCUS	544/548, 1.06 (0.95–1.20)	**664/864, 1.89 (1.71–2.08)**	**472/1435, 0.75 (0.68–0.83)**
CIN2	49/66, 0.80 (0.55–1.15)	**62/84, 1.81 (1.31–2.51)**	33/73, 1.03 (0.68–1.56)
⩾CIN3	161/165, 1.05 (0.84–1.30)	**176/273, 1.58 (1.31–1.91)**	132/259, 1.16 (0.94–1.43)
CIN treatments	244/275, 0.95 (0.80–1.13)	**252/360, 1.72 (1.47–2.02)**	188/367, 1.17 (0.98–1.39)
<CIN2	168/190, 0.95 (0.77–1.16)	**238/258, 2.27 (1.90–2.70)**	**181/579, 0.71 (0.60–0.84)**
False positive for ⩾CIN2	334/317, 1.13 (0.97–1.31)	**426/507, 2.06 (1.82–2.34)**	**307/1103, 0.64 (0.56–0.72)**
False positive for ⩾CIN3	383/383, 1.07 (0.93–1.23)	**488/591, 2.03 (1.80–2.28)**	**340/1176, 0.66 (0.59–0.74)**
PPV for ⩾CIN2	39%/42%, 0.92 (0.79–1.06)	**36%/41%, 0.87 (0.76–0.99)**	**35%/23%, 1.51 (1.29–1.76)**
PPV for ⩾CIN3	30%/30%, 0.98 (0.82–1.18)	**27%/32%, 0.84 (0.71–0.98)**	**28%/18%, 1.55 (1.29–1.86)**
45–59 years	19 901/23 253	5540/16 355	13 934/27 404
⩾ASCUS	**253/352, 0.84 (0.72–0.99)**	**263/415, 1.87 (1.61–2.18)**	**180/922, 0.38 (0.33–0.45)**
CIN2	14/14, 1.17 (0.56–2.45)	6/10, 1.77 (0.64–4.87)	12/17, 1.39 (0.66–2.91)
⩾CIN3	39/43, 1.06 (0.69–1.63)	14/63, 0.66 (0.37–1.17)	14/48, 0.57 (0.32–1.04)
CIN treatments	58/74, 0.92 (0.65–1.29)	25/86, 0.86 (0.55–1.34)	34/86, 0.78 (0.52–1.16)
<CIN2	**106/190, 0.65 (0.51–0.83)**	85/206, 1.22 (0.95–1.57)	**110/556, 0.39 (0.32–0.48)**
False positive for ⩾CIN2	**200/295, 0.79 (0.66–0.95)**	**243/342, 2.10 (1.78–2.47)**	**154/857, 0.35 (0.30–0.42)**
False positive for ⩾CIN3	**214/309, 0.81 (0.68–0.96)**	**249/352, 2.09 (1.78–2.45)**	**166/874, 0.37 (0.32–0.44)**
PPV for ⩾CIN2	21%/16%, 1.29 (0.92–1.81)	**8%/18%, 0.43 (0.27–0.69)**	**14%/7%, 2.05 (1.34–3.14)**
PPV for ⩾CIN3	15%/12%, 1.26 (0.84–1.89)	**5%/15%, 0.35 (0.20–0.61)**	8%/5%, 1.49 (0.84–2.65)

Abbreviations: ASCUS = atypical squamous cells of undetermined significance; CI = confidence interval; CIN = cervical intraepithelial neoplasia; CPH M = Copenhagen Municipality; HC2 = Hybrid Capture 2; N_{after} = last phase; N_{before} = phase 1; PPV = positive predictive value; RP = relative proportion; triage = in case of ASCUS at age ⩾30 years. Bold signifies significant change comparing the last phase ('after') with phase 1 ('before').
[a]Compared with manually read conventional cytology (baseline).
[b]N_{after}/N_{before}, RR (95% CI).
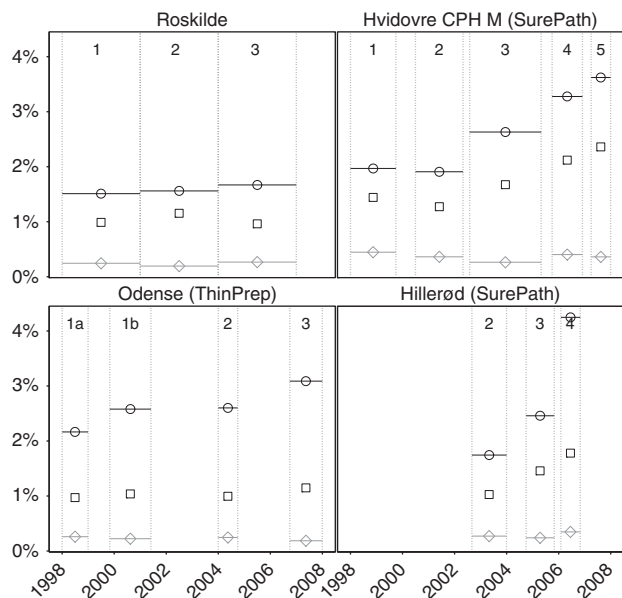[c]N_{after}/N_{before}, RR (95% CI).
[d]N_{after}/N_{before}, RR (95% CI).

Figure 1. Frequency of histologically confirmed ⩾CIN2, by laboratory and phase. Roskilde: manually read conventional cytology in all phases. Hvidovre and Hillerød: SurePath/FocalPoint reading and liquid-based cytology technologies. Odense: ThinPrep reading and liquid-based cytology technologies. ○, 23–29 years; □, 30–44 years; ◇, 45–59 years. Phases as described in Table 1. CPH M, Copenhagen Municipality.

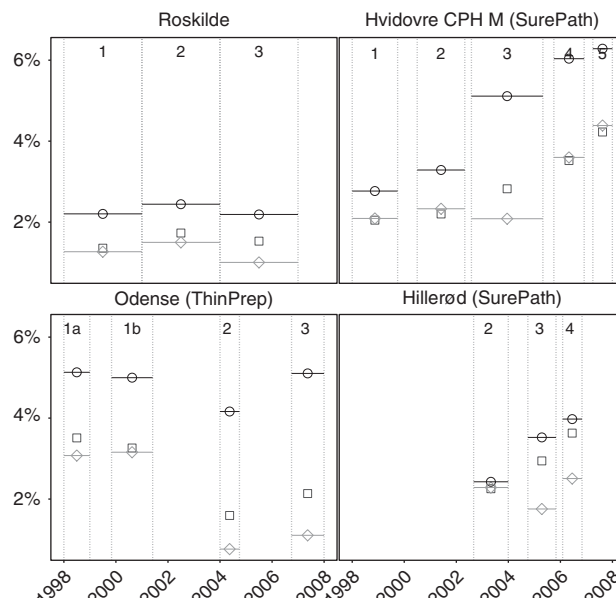
Figure 3. Frequency of false-positive tests for ⩾CIN2 (samples with abnormal cytology that were not followed by a histological diagnosis of ⩾CIN2), by laboratory and phase. Roskilde: manually read conventional cytology in all phases. Hvidovre and Hillerød: SurePath/FocalPoint reading and liquid-based cytology technologies. Odense: ThinPrep reading and liquid-based cytology technologies. ○, 23–29 years; □, 30–44 years; ◇, 45–59 years. Phases as described in Table 1. CPH M, Copenhagen Municipality.
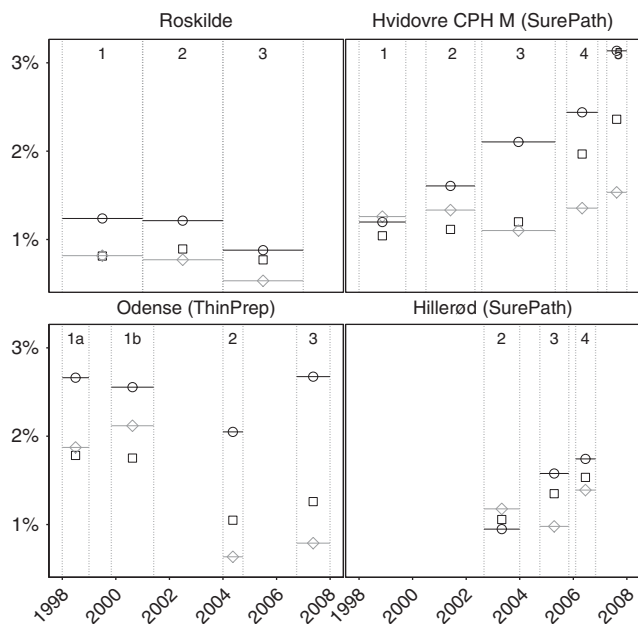

Figure 2. Frequency of histologically confirmed <CIN2, by laboratory and phase. Roskilde: manually read conventional cytology in all phases. Hvidovre and Hillerød: SurePath/FocalPoint reading and liquid-based cytology technologies. Odense: ThinPrep reading and liquid-based cytology technologies. ○, 23–29 years; □, 30–44 years, and ◇, 45–59 years. Phases as described in Table 1. CPH M, Copenhagen Municipality.

Strengths and weaknesses. We included routine samples from women targeted by the Danish screening programme. Abnormalities were verified through four nation-wide registers. Abnormal cytology was defined as any abnormality that would trigger follow-up,

either through repeated testing or a referral for colposcopy. Histology was ascertained practically throughout the whole three-yearly screening round, and only periods with highly complete histological registration were included. Compared with other studies of routine screening, the proportion of women with histological verification of ⩾ASCUS was relatively high. We excluded all piloting and implementation periods. Although some remaining learning curve effects cannot be entirely dismissed (Kirschner *et al*, 2006), the outcomes of our study should be representative for a 'normal' use of the evaluated technologies.

As a limitation, it should be emphasised that ThinPrep data were based on a single laboratory. This laboratory started with a high proportion of cytological abnormalities (Rask *et al*, 2014), possibly signifying a relatively high sensitivity and low specificity for detecting high-grade CIN to begin with. In this laboratory, a clear advantage of ThinPrep technologies was an improvement in screening specificity.

Inferences regarding causation should be made cautiously. A competing explanation for the observed changes could be a changed risk of cervical lesions. This is, however, unlikely. First, the changes in the laboratory that continuously used manually read conventional cytology were of a substantially smaller magnitude compared with in the laboratories with changing technologies. Second, the laboratories served catchment areas in relatively close geographical proximity, and no change during the study period with a potentially differential effect on the background risk of cervical cancer could be identified.

Our study covered a 10-year period plus 2.5-year follow-up, during which the women's sociodemographic characteristics and screening histories may have changed. Ideally, these would have been adjusted for in the analysis. The age structure changed very little, and all analyses were age-stratified. Given Denmark's homogeneity, any changes in the sociodemographic factors would affect Roskilde's catchment area in a similar way as those of other laboratories.

In our analysis, we focused on relative changes. The catchment area of Hvidovre to a higher extent included an urban population, thus absolute age-specific levels of disease detection may not have been comparable across the four laboratories. Hence, technologies were compared strictly within individual laboratories.

Clinical implications. The combination of screening and triage tests should offer the highest sensitivity for high-grade CIN and an acceptable PPV of an immediate referral to colposcopy. For reasons of cost, logistics, and women's discomfort, it is preferable to perform all screening and triage tests on the same sample. A consideration of an optimal medium for sample storage is, therefore, going to have a role also when the switch is going to be made from the present cytology-based screening with HPV triage to the imminent HPV-based screening with cytology triage. Critics have claimed that SurePath LBC medium might be unsuitable for HPV testing (Naryshkin and Austin, 2012), and none of the US Food and Drug Administration approvals for HPV assays were granted for samples stored in SurePath. Only few HPV studies evaluated SurePath samples, in particular the Danish Horizon study evaluating APTIMA, cobas, HC2, and CLART assays (Rebolj *et al*, 2013, 2014a, 2014b). The challenge with SurePath in HPV testing is its formaldehyde content, which induces covalent bindings between protein structures and the HPV's genetic material. These render the genetic material inaccessible to enzyme-driven amplification or detection. However, a preheating step reverses the bindings (Steinau *et al*, 2011). As a result, invalid HPV test results that would suggest inaccessible genetic material tend to be infrequent (Rebolj *et al*, 2014a). Against this background, the improved detection of high-grade CIN in SurePath samples observed in our study might be relevant also for HPV-based screening with cytology triage.

When changes are made to screening programmes, it is worth keeping in mind the more general finding from this study, in that replacing or adjusting a screening test can cause a shift in the population who tests positive, is referred for further follow-up, and finally treated. More sensitive screening methods may shift the detection toward smaller CIN lesions with a lower potential for progression (Schiffman and Rodriguez, 2008). In our study, an increased detection with LBC and/or computer-assisted reading with either brand was observed particularly at relatively young ages, when lesions less likely progress (van Oortmarssen and Habbema, 1991). To optimise screening recommendations with respect to the technology, future analyses of interval cervical cancers should determine to what extent the observed increases in the sensitivity of cytology represented overtreatment or a reduction in the burden of cervical cancer.

In conclusion, this study confirmed our earlier findings that modern cytological technologies have not been neutral with respect to the detection of cervical disease. In the Danish setting, the trends in the sensitivity and specificity depended on the type and the brand of the technology, and the age of the screened women. In essence, SurePath-based technology increased the sensitivity of cytology for high-grade cervical lesions predominantly at younger ages, whereas ThinPrep-based technology increased the specificity predominantly at older ages.

CONFLICT OF INTEREST

JR, MvB, and BK declare no conflict of interest. MR, JB, CR, and EL are undertaking a comparative study of new-generation HPV assays, involving collaboration with Roche, Genomica, Qiagen, and Hologic, and a self-sampling pilot involving collaboration with Genomica, BD, and Rovers. MR and her former employer received honoraria from Qiagen for lectures on her behalf. KR was invited by BD to present her work at an international conference, for which she received no honorarium. JB used to serve as a paid advisor to Roche, is a paid advisor to Genomica, and received honoraria from Hologic, Roche, Qiagen, Genomica, and BD Diagnostics for lectures. He is a principal investigator on studies funded by BD Diagnostics. CR served as an unpaid advisor to Roche. EL served as an unpaid advisor to Hologic and Norchip. Hvidovre Hospital holds a recompense agreement with Genomica on a KRAS/BRAF diagnostic system. None of the authors was compensated for their work on this project, holds stock, or received bonuses from any of the manufacturers.

AUTHOR CONTRIBUTIONS

Design of the study: MR, EL; analysis of the data: MR, JR; visual representation of the data: JR; interpretation of the results: all co-authors; drafting of the manuscript: MR, JR; critical revisions of the manuscript: all co-authors; decision to submit: all coauthors.

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APPENDIX

Table A1. Completeness of 2.5-year follow-up after an ⩾ASCUS primary sample[a]

	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5
Included samples/all primary samples					
Roskilde	53 979/56 769 (95%)	49 856/51 902 (96%)	47 300/48 717 (97%)	—	—
Hvidovre (CPH M)	62 644/73 551 (85%)	59 274/67 311 (88%)	94 541/105 483 (90%)	43 002/47 164 (91%)	23 849/25 587 (93%)
Hvidovre (FRB M)	—	9385/10 540 (89%)	17 643/19 567 (90%)	7018/7639 (92%)	4794/5142 (93%)
Hillerød	—	28 888/29 928 (97%)	24 593/25 631 (96%)	18 434/19 178 (96%)	—
Odense	74 522/76 528 (97%)[b]	20 921/21 251 (98%)	33 614/34 066 (99%)	—	—
No follow-up/⩾ASCUS					
Roskilde	78/1173 (7%)	64/1251 (5%)	51/1012 (5%)	—	—
Hvidovre (CPH M)	111/2299 (5%)	87/2307 (4%)	343/4832 (7%)	257/2751 (9%)	120/1742 (7%)
Hvidovre (FRB M)	—	9/361 (2%)	56/830 (7%)	43/420 (10%)	23/352 (7%)
Hillerød	—	22/878 (3%)	26/865 (3%)	30/843 (4%)	—
Odense	83/3423 (2%)[c]	19/536 (4%)	57/1087 (5%)	—	—
No histology follow-up/⩾ASCUS					
Roskilde	225/1173 (19%)	355/1251 (28%)	282/1012 (28%)	—	—
Hvidovre (CPH M)	612/2299 (27%)	671/2307 (29%)	1504/4832 (31%)	767/2751 (28%)	485/1742 (28%)
Hvidovre (FRB M)	—	116/361 (32%)	263/830 (32%)	114/420 (27%)	88/352 (25%)
Hillerød	—	320/878 (36%)	287/865 (33%)	280/843 (33%)	—
Odense	1093/3423 (32%)[d]	108/536 (20%)	242/1087 (22%)	—	—

Abbreviations: ASCUS = atypical squamous cells of undetermined significance; CPH M = Copenhagen Municipality; FRB M = Frederiksberg Municipality.
[a]Primary screening samples included in the study, by laboratory and phase, women aged 23–59 years.
[b]Phase 1a: 29 293/30 280 (97%). Phase 1b: 45 229/46 248 (98%).
[c]Phase 1a: 47/1374 (3%). Phase 1b: 36/2049 (2%).
[d]Phase 1a: 453/1374 (33%). Phase 1b: 640/2049 (31%).

Table A2. Distribution of age groups by phase and laboratory

	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5
Roskilde					
23–29 years	7350 (14%)	6346 (13%)	5572 (12%)	—	—
30–44 years	23 376 (43%)	21 843 (44%)	21 827 (46%)	—	—
45–59 years	23 253 (43%)	21 667 (43%)	19 901 (42%)	—	—
Total	53 797 (100%)	49 856 (100%)	47 300 (100%)	—	—
Mean age (s.d.)	41.8 (10.1)	42.3 (10.2)	42.2 (10.0)	—	—
Hvidovre (CPH M)					
23–29 years	21 536 (34%)	21 537 (36%)	33 450 (35%)	13 733 (32%)	8228 (35%)
30–44 years	24 753 (40%)	21 987 (37%)	37 576 (40%)	18 348 (43%)	10 081 (42%)
45–59 years	16 355 (26%)	15 750 (27%)	23 515 (25%)	10 921 (25%)	5540 (23%)
Total	62 644 (100%)	59 274 (100%)	94 541 (100%)	43 002 (100%)	23 849 (100%)
Mean age (s.d.)	36.4 (10.4)	36.4 (10.7)	36.3 (10.6)	36.7 (10.4)	36.1 (10.4)
Hvidove (FRB M)					
23–29 years	—	2413 (26%)	4949 (28%)	1909 (27%)	1238 (26%)
30–44 years	—	3683 (39%)	7225 (41%)	3071 (44%)	2164 (45%)
45–59 years	—	3289 (35%)	5460 (31%)	2038 (29%)	1392 (29%)
Total	—	9385 (100%)	17 634 (100%)	7018 (100%)	4794 (100%)
Mean age (s.d.)	—	39.1 (11.0)	38.3 (11.0)	38.0 (10.8)	38.2 (10.7)
Hillerød					
23–29 years	—	2637 (9%)	2725 (11%)	1836 (10%)	—
30–44 years	—	13 342 (46%)	11 043 (45%)	8541 (46%)	—
45–59 years	—	12 909 (45%)	10 825 (44%)	8057 (44%)	—
Total	—	28 888 (100%)	24 593 (100%)	18 434 (100%)	—
Mean age (s.d.)	—	42.9 (9.6)	42.7 (10.0)	42.7 (9.6)	—
Odense					
23–29 years	14 299 (19%)	3075 (15%)	5310 (16%)	—	—
30–44 years	32 819 (44%)	9342 (45%)	14 370 (43%)	—	—
45–59 years	27 404 (37%)	8504 (41%)	13 934 (41%)	—	—
Total	74 522 (100%)	20 921 (100%)	33 614 (100%)	—	—
Mean age (s.d.)	40.1 (10.4)	41.4 (10.2)	41.5 (10.3)	—	—

Abbreviations: CPH M = Copenhagen Municipality; FRB M = Frederiksberg Municipality.

Table A3. Laboratory with manual reading of conventional cytology throughout the study period (Roskilde)[a]		
	Phase 2 (baseline) vs phase 1 (baseline)	Phase 3 (baseline) vs phase 2 (baseline)
Change in the technology	None	None
Same technology in both phases	Conventional cytology, manual reading, cytology triage of ASCUS	Conventional cytology, manual reading, cytology triage of ASCUS
23–59 years	49 856/53 979	47 300/49 856
⩾ASCUS	**1251/1173, 1.15 (1.07–1.25)**	**1012/1251, 0.85 (0.79–0.93)**
CIN2	104/118, 0.95 (0.73–1.24)	85/104, 0.86 (0.65–1.15)
⩾CIN3	289/281, 1.11 (0.95–1.31)	271/289, 0.99 (0.84–1.17)
CIN treatments	491/482, 1.10 (0.97–1.25)	**405/491, 0.87 (0.76–0.99)**
<CIN2	439/471, 1.01 (0.89–1.15)	**323/439, 0.78 (0.67–0.89)**
False positive for ⩾CIN2	**858/774, 1.20 (1.09–1.32)**	**656/858, 0.81 (0.73–0.89)**
False positive for ⩾CIN3	**962/892, 1.17 (1.07–1.28)**	**741/962, 0.81 (0.74–0.89)**
PPV for ⩾CIN2	31%/34%, 0.92 (0.82–1.04)	35%/31%, 1.12 (1.00–1.26)
PPV for ⩾CIN3	23%/24%, 0.96 (0.84–1.11)	**27%/23%, 1.16 (1.00–1.34)**
23–29 years	6346/7350	5572/6346
⩾ASCUS	254/273, 1.08 (0.91–1.27)	215/254, 0.96 (0.81–1.15)
CIN2	24/38, 0.73 (0.44–1.22)	22/24, 1.04 (0.59–1.86)
⩾CIN3	75/73, 1.19 (0.86–1.64)	71/75, 1.08 (0.78–1.49)
CIN treatments	119/133, 1.04 (0.81–1.32)	103/119, 0.99 (0.76–1.28)
<CIN2	77/91, 0.98 (0.72–1.33)	49/77, 0.72 (0.51–1.04)
False positive for ⩾CIN2	155/162, 1.11 (0.89–1.38)	122/155, 0.90 (0.71–1.13)
False positive for ⩾CIN3	179/200, 1.04 (0.85–1.26)	144/179, 0.92 (0.74–1.14)
PPV for ⩾CIN2	39%/41%, 0.96 (0.78–1.18)	43%/39%, 1.11 (0.89–1.38)
PPV for ⩾CIN3	30%/27%, 1.10 (0.84–1.45)	33%/30%, 1.12 (0.85–1.46)
30–44 years	21 843/23 376	21 827/21 843
⩾ASCUS	**630/548, 1.23 (1.10–1.38)**	**544/630, 0.86 (0.77–0.97)**
CIN2	72/66, 1.17 (0.84–1.63)	**49/72, 0.68 (0.47–0.98)**
⩾CIN3	180/165, 1.17 (0.95–1.44)	161/180, 0.90 (0.72–1.11)
CIN treatments	**305/375, 1.19 (1.01–1.40)**	**244/305, 0.80 (0.68–0.95)**
<CIN2	195/190, 1.10 (0.90–1.34)	168/195, 0.86 (0.70–1.06)
False positive for ⩾CIN2	**378/317, 1.28 (1.10–1.48)**	334/378, 0.88 (0.76–1.02)
False positive for ⩾CIN3	**450/383, 1.26 (1.10–1.44)**	**383/450, 0.85 (0.74–0.97)**
PPV for ⩾CIN2	40%/42%, 0.95 (0.83–1.09)	39%/40%, 0.97 (0.84–1.11)
PPV for ⩾CIN3	29%/30%, 0.95 (0.79–1.13)	30%/29%, 1.04 (0.87–1.24)
45–59 years	21 667/23 253	19 901/21 667
⩾ASCUS	367/352, 1.12 (0.97–1.29)	**253/367, 0.75 (0.64–0.88)**
CIN2	8/14, 0.61 (0.26–1.46)	14/8, 1.91 (0.80–4.54)
⩾CIN3	34/43, 0.85 (0.54–1.33)	39/34, 1.25 (0.79–1.98)
CIN treatments	67/74, 0.97 (0.70–1.35)	58/67, 0.94 (0.66–1.34)
<CIN2	167/190, 0.94 (0.77–1.16)	**106/167, 0.69 (0.54–0.88)**
False positive for ⩾CIN2	**325/295, 1.18 (1.01–1.38)**	**200/325, 0.67 (0.56–0.80)**
False positive for ⩾CIN3	333/309, 1.16 (0.99–1.35)	**214/333, 0.70 (0.59–0.83)**
PPV for ⩾CIN2	11%/16%, 0.71 (0.49–1.02)	**21%/11%, 1.83 (1.26–2.66)**
PPV for ⩾CIN3	9%/12%, 0.76 (0.50–1.16)	**15%/9%, 1.66 (1.08–2.56)**

Abbreviations: ASCUS = atypical squamous cells of undetermined significance; CIN = cervical intraepithelial neoplasia; PPV = positive predictive value; triage = in case of ASCUS at age ⩾30 years. Bold signifies significant change comparing the two phases.
[a]Comparison of outcomes, by age group and phase.

Table A4. Laboratory with SurePath cytological technology (Hvidovre/Copenhagen Municipality)[a]				
	Phase 2 *vs* phase 1	**Phase 3 *vs* phase 2**	**Phase 4 *vs* phase 3**	**Phase 5 *vs* phase 4**
Change in the technology	FocalPoint Slide Profiler 50% cutoff	SurePath LBC	FocalPoint Slide Profiler cutoff decreased to 25%, HC2 triage of ASCUS	FocalPoint GS Imaging System
Same technology in both phases	Conventional cytology, cytology triage of ASCUS	FocalPoint Slide Profiler 50% cutoff, cytology triage of ASCUS	SurePath LBC	SurePath LBC, FocalPoint Slide Profiler 25% cutoff, HC2 triage of ASCUS
23–59 years	59 274/62 644	94 541/59 274	43 002/94 541	23 849/43 002
≥ASCUS	2307/2299, 1.06 (1.00–1.12)	**4832/2307, 1.31 (1.25–1.38)**	**2751/4832, 1.25 (1.20–1.31)**	**1742/2751, 1.14 (1.08–1.21)**
CIN2	201/230, 0.92 (0.76–1.12)	**423/201, 1.32 (1.12–1.56)**	**242/423, 1.26 (1.07–1.47)**	162/242, 1.21 (0.99–1.47)
≥CIN3	547/624, 0.93 (0.83–1.04)	**1148/547, 1.32 (1.19–1.46)**	**641/1148, 1.23 (1.12–1.35)**	394/641, 1.11 (0.98–1.26)
CIN treatments	828/857, 1.02 (0.93–1.12)	**1780/828, 1.35 (1.24–1.46)**	**959/1780, 1.18 (1.10–1.28)**	**603/959, 1.13 (1.03–1.25)**
<CIN2	**801/722, 1.17 (1.06–1.30)**	**1414/801, 1.11 (1.02–1.21)**	**844/1414, 1.31 (1.21–1.43)**	**581/844, 1.24 (1.12–1.38)**
False positive for ≥CIN2	**1559/1445, 1.14 (1.06–1.22)**	**3261/1559, 1.31 (1.24–1.39)**	**1868/3261, 1.26 (1.19–1.33)**	**1186/1868, 1.14 (1.07–1.23)**
False positive for ≥CIN3	**1760/1675, 1.11 (1.04–1.19)**	**3684/1760, 1.31 (1.24–1.39)**	**2110/3684, 1.26 (1.20–1.33)**	**1348/2110, 1.15 (1.08–1.23)**
PPV for ≥CIN2	**32%/37%, 0.87 (0.81–0.94)**	33%/32%, 1.00 (0.93–1.08)	32%/33%, 0.99 (0.92–1.06)	32%/32%, 0.99 (0.91–1.09)
PPV for ≥CIN3	**24%/27%, 0.87 (0.79–0.96)**	24%/24%, 1.00 (0.92–1.10)	23%/24%, 0.98 (0.90–1.07)	23%/23%, 0.97 (0.87–1.08)
23–29 years	21 537/21 536	33 450/21 537	13 733/33 450	8228/13 733
≥ASCUS	**1119/1020, 1.10 (1.01–1.19)**	**2590/1119, 1.49 (1.39–1.60)**	**1279/2590, 1.20 (1.13–1.28)**	815/1279, 1.06 (0.98–1.16)
CIN2	120/136, 0.88 (0.69–1.13)	**251/120, 1.35 (1.08–1.67)**	**134/251, 1.30 (1.06–1.60)**	94/134, 1.17 (0.90–1.52)
≥CIN3	291/288, 1.01 (0.86–1.19)	**629/291, 1.39 (1.21–1.60)**	**316/629, 1.22 (1.07–1.40)**	204/316, 1.08 (0.91–1.28)
CIN treatments	449/411, 1.09 (0.96–1.25)	**996/449, 1.43 (1.28–1.59)**	**476/996, 1.16 (1.05–1.30)**	326/476, 1.14 (1.00–1.31)
<CIN2	**346/258, 1.34 (1.14–1.57)**	**704/346, 1.31 (1.15–1.49)**	**335/704, 1.16 (1.02–1.32)**	**258/335, 1.29 (1.10–1.51)**
False positive for ≥CIN2	**708/596, 1.19 (1.07–1.32)**	**1710/708, 1.56 (1.43–1.69)**	**829/1710, 1.18 (1.09–1.28)**	517/829, 1.04 (0.94–1.16)
False positive for ≥CIN3	**828/732, 1.13 (1.03–1.25)**	**1961/828, 1.52 (1.41–1.65)**	**963/1961, 1.20 (1.11–1.29)**	611/963, 1.06 (0.96–1.17)
PPV for ≥CIN2	**37%/42%, 0.88 (0.79–0.98)**	34%/37%, 0.93 (0.84–1.02)	35%/34%, 1.04 (0.94–1.14)	37%/35%, 1.04 (0.92–1.17)
PPV for ≥CIN3	26%/28%, 0.92 (0.80–1.06)	24%/26%, 0.93 (0.83–1.05)	25%/24%, 1.02 (0.90–1.14)	25%/25%, 1.01 (0.87–1.18)
30–44 years	21 987/24 753	37 576/21 987	18 348/37 576	10 081/18 348
≥ASCUS	764/864, 1.00 (0.90–1.10)	**1690/764, 1.29 (1.19–1.41)**	**1035/1690, 1.25 (1.16–1.35)**	**664/1035, 1.17 (1.06–1.28)**
CIN2	63/84, 0.84 (0.61–1.17)	**154/63, 1.43 (1.07–1.92)**	**98/154, 1.30 (1.01–1.68)**	62/98, 1.15 (0.84–1.58)
≥CIN3	217/273, 0.89 (0.75–1.07)	**475/217, 1.28 (1.09–1.50)**	**291/475, 1.25 (1.09–1.45)**	176/291, 1.10 (0.91–1.33)
CIN treatments	308/360, 0.96 (0.83–1.12)	**702/308, 1.33 (1.17–1.52)**	**430/702, 1.25 (1.11–1.41)**	252/430, 1.07 (0.91–1.24)
<CIN2	245/258, 1.07 (0.90–1.27)	451/245, 1.08 (0.92–1.26)	**361/451, 1.64 (1.43–1.88)**	**238/361, 1.20 (1.02–1.41)**
False positive for ≥CIN2	484/507, 1.07 (0.95–1.22)	**1061/484, 1.28 (1.15–1.43)**	**646/1061, 1.25 (1.13–1.37)**	**426/646, 1.20 (1.06–1.35)**
False positive for ≥CIN3	547/591, 1.04 (0.93–1.17)	**1215/547, 1.30 (1.18–1.44)**	**744/1215, 1.25 (1.15–1.37)**	**488/744, 1.19 (1.07–1.33)**
PPV for ≥CIN2	37%/41%, 0.89 (0.78–1.00)	37%/37%, 1.02 (0.91–1.14)	38%/37%, 1.01 (0.91–1.12)	36%/38%, 0.95 (0.84–1.08)
PPV for ≥CIN3	28%/32%, 0.90 (0.77–1.04)	28%/28%, 0.99 (0.86–1.13)	28%/28%, 1.00 (0.88–1.13)	27%/28%, 0.94 (0.80–1.11)
45–59 years	15 750/16 355	23 515/15 750	10 921/23 515	5540/10 921
≥ASCUS	424/415, 1.06 (0.93–1.21)	**552/424, 0.87 (0.77–0.99)**	**437/552, 1.70 (1.51–1.93)**	**263/437, 1.19 (1.02–1.38)**
CIN2	18/10, 1.87 (0.86–4.05)	18/18, 0.67 (0.35–1.29)	10/18, 1.20 (0.55–2.59)	6/10, 1.18 (0.43–3.25)
≥CIN3	**39/63, 0.64 (0.43–0.96)**	44/39, 0.76 (0.49–1.16)	**34/44, 1.66 (1.06–2.60)**	14/34, 0.81 (0.44–1.51)
CIN treatments	71/86, 0.86 (0.63–1.17)	82/71, 0.77 (0.56–1.06)	53/82, 1.39 (0.99–1.96)	25/53, 0.93 (0.58–1.49)
<CIN2	210/206, 1.06 (0.87–1.28)	**259/210, 0.83 (0.69–0.99)**	**148/259, 1.23 (1.01–1.50)**	85/148, 1.13 (0.87–1.48)
False positive for ≥CIN2	367/342, 1.11 (0.96–1.29)	490/367, 0.89 (0.78–1.02)	**393/490, 1.73 (1.52–1.97)**	**243/393, 1.22 (1.04–1.43)**
False positive for ≥CIN3	385/352, 1.14 (0.98–1.31)	508/385, 0.88 (0.78–1.01)	**403/508, 1.71 (1.50–1.94)**	**249/403, 1.22 (1.04–1.42)**
PPV for ≥CIN2	13%/18%, 0.76 (0.56–1.05)	11%/13%, 0.84 (0.60–1.17)	10%/11%, 0.90 (0.62–1.29)	8%/10%, 0.76 (0.46–1.25)
PPV for ≥CIN3	**9%/15%, 0.61 (0.42–0.88)**	8%/9%, 0.87 (0.57–1.31)	8%/8%, 0.98 (0.64–1.50)	5%/8%, 0.68 (0.37–1.25)

Abbreviations: ASCUS = atypical squamous cells of undetermined significance; CIN = cervical intraepithelial neoplasia; HC2 = Hybrid Capture 2; PPV = positive predictive value; triage = in case of ASCUS at age ≥30 years. Bold signifies significant change comparing the two phases.
[a]Comparison of outcomes, by age group and phase.

Table A5. Laboratory with SurePath cytological technology (Hvidovre/Frederiksberg Municipality)[a]			
	Phase 3 vs phase 2	Phase 4 vs phase 3	Phase 5 vs phase 4
Change in the technology	SurePath LBC	FocalPoint Slide Profiler cutoff decreased to 25%, HC2 triage of ASCUS	FocalPoint GS Imaging System
Same technology in both phases	FocalPoint Slide Profiler 50% cutoff, cytology triage of ASCUS	SurePath LBC	SurePath LBC, FocalPoint Slide Profiler 25% cutoff, HC2 triage of ASCUS
23–59 years	17 634/9385	7018/17 634	4794/7018
≥ASCUS	**830/361, 1.22 (1.08–1.38)**	**420/830, 1.27 (1.13–1.43)**	**352/420, 1.23 (1.07–1.41)**
CIN2	**77/26, 1.58 (1.01–2.46)**	**51/77, 1.66 (1.17–2.37)**	39/51, 1.12 (0.74–1.70)
≥CIN3	195/97, 1.07 (0.84–1.36)	**107/195, 1.38 (1.09–1.74)**	80/107, 1.09 (0.82–1.46)
CIN treatments	304/134, 1.21 (0.99–1.48)	**169/304, 1.40 (1.16–1.68)**	140/169, 1.21 (0.97–1.51)
<CIN2	239/113, 1.13 (0.90–1.41)	105/239, 1.10 (0.88–1.39)	**122/105, 1.70 (1.31–2.20)**
False positive for ≥CIN2	**558/238, 1.25 (1.07–1.45)**	**262/558, 1.18 (1.02–1.36)**	**233/262, 1.30 (1.10–1.55)**
False positive for ≥CIN3	**635/264, 1.28 (1.11–1.47)**	**313/635, 1.24 (1.08–1.41)**	**272/313, 1.27 (1.09–1.49)**
PPV for ≥CIN2	33%/34%, 0.96 (0.81–1.14)	38%/33%, 1.15 (0.98–1.34)	34%/38%, 0.90 (0.74–1.09)
PPV for CIN3	23%/27%, 0.87 (0.71–1.08)	25%/23%, 1.08 (0.88–1.33)	23%/25%, 0.89 (0.69–1.15)
23–29 years	4949/2413	1909/4949	1238/1909
≥ASCUS	**367/133, 1.35 (1.11–1.63)**	**174/367, 1.23 (1.03–1.46)**	135/174, 1.20 (0.97–1.48)
CIN2	45/19, 1.15 (0.68–1.97)	21/45, 1.21 (0.72–2.03)	24/21, 1.76 (0.99–3.15)
≥CIN3	97/36, 1.31 (0.90–1.92)	**56/97, 1.50 (1.08–2.07)**	37/56, 1.02 (0.68–1.53)
CIN treatments	**156/55, 1.38 (1.02–1.87)**	**81/156, 1.35 (1.03–1.75)**	66/81, 1.26 (0.92–1.73)
<CIN2	92/30, 1.50 (0.99–2.25)	34/92, 0.96 (0.65–1.41)	**38/34, 1.72 (1.09–2.72)**
False positive for ≥CIN2	**225/78, 1.41 (1.09–1.81)**	97/225, 1.12 (0.89–1.41)	74/97, 1.18 (0.88–1.58)
False positive for ≥CIN3	**270/97, 1.36 (1.08–1.70)**	118/270, 1.13 (0.92–1.40)	98/118, 1.28 (0.99–1.66)
PPV for ≥CIN2	39%/41%, 0.94 (0.74–1.19)	44%/39%, 1.14 (0.93–1.41)	45%/44%, 1.02 (0.80–1.31)
PPV for CIN3	26%/27%, 0.98 (0.70–1.35)	32%/26%, 1.22 (0.92–1.60)	27%/32%, 0.85 (0.60–1.21)
30–44 years	7225/3683	3071/7225	2164/3071
≥ASCUS	**334/136, 1.25 (1.03–1.52)**	**176/334, 1.24 (1.04–1.48)**	151/176, 1.22 (0.99–1.50)
CIN2	**31/5, 3.16 (1.23–8.12)**	**28/31, 2.12 (1.28–3.54)**	13/28, 0.66 (0.34–1.27)
≥CIN3	82/44, 0.95 (0.66–1.37)	**50/82, 1.43 (1.01–2.03)**	42/50, 1.19 (0.79–1.79)
CIN treatments	129/55, 1.20 (0.87–1.64)	**85/129, 1.55 (1.18–2.03)**	67/85, 1.12 (0.82–1.53)
<CIN2	94/42, 1.14 (0.79–1.64)	49/94, 1.23 (0.87–1.73)	**60/49, 1.74 (1.20–2.52)**
False positive for ≥CIN2	**221/87, 1.29 (1.01–1.65)**	98/221, 1.04 (0.83–1.32)	**96/98, 1.39 (1.05–1.83)**
False positive for ≥CIN3	**252/92, 1.40 (1.10–1.77)**	126/252, 1.18 (0.95–1.45)	109/126, 1.23 (0.96–1.58)
PPV for ≥CIN2	34%/36%, 0.94 (0.72–1.23)	**44%/34%, 1.31 (1.05–1.64)**	36%/44%, 0.82 (0.63–1.07)
PPV for CIN3	25%/32%, 0.76 (0.56–1.03)	28%/25%, 1.16 (0.86–1.56)	28%/28%, 0.98 (0.69–1.39)
45–59 years	5460/3289	2038/5460	1392/2038
≥ASCUS	129/92, 0.84 (0.65–1.10)	**70/129, 1.45 (1.09–1.94)**	66/70, 1.38 (0.99–1.92)
CIN2	1/2, 0.30 (0.03–3.32)	2/1, 5.36 (0.49–59.06)	2/2, 1.46 (0.21–10.38)
≥CIN3	16/17, 0.57 (0.29–1.12)	1/16, 0.17 (0.02–1.26)	1/1, 1.46 (0.09–23.39)
CIN treatments	**19/24, 0.48 (0.26–0.87)**	3/19, 0.42 (0.13–1.43)	7/3, 3.42 (0.88–13.19)
<CIN2	53/41, 0.78 (0.52–1.17)	22/53, 1.11 (0.68–1.82)	24/22, 1.60 (0.90–2.84)
False positive for ≥CIN2	112/73, 0.92 (0.69–1.24)	**67/112, 1.60 (1.19–2.16)**	63/67, 1.38 (0.98–1.93)
False positive for ≥CIN3	113/75, 0.91 (0.68–1.21)	**69/113, 1.64 (1.22–2.20)**	65/69, 1.38 (0.99–1.92)
PPV for ≥CIN2	13%/21%, 0.64 (0.35–1.16)	4%/13%, 0.33 (0.10–1.07)	5%/4%, 1.06 (0.22–5.07)
PPV for CIN3	12%/18%, 0.67 (0.36–1.26)	**1%/12%, 0.12 (0.02–0.85)**	2%/1%, 1.06 (0.07–16.61)

Abbreviations: ASCUS = atypical squamous cells of undetermined significance; CIN = cervical intraepithelial neoplasia; HC2 = Hybrid Capture 2; PPV = positive predictive value; triage = in case of ASCUS at age ≥30 years. Bold signifies significant change comparing the two phases.
[a]Comparison of outcomes, by age group and phase.

Table A6. Laboratory with SurePath cytological technology (Hillerød)[a]		
	Phase 3 vs phase 2	**Phase 4 vs phase 3**
Change in the technology	SurePath LBC, FocalPoint Slide Profiler cutoff decreased to 25%	FocalPoint GS Imaging System
Same technology in both phases	Cytology triage of ASCUS	SurePath LBC, Focal Point Slide Profiler 25% cutoff, cytology triage of ASCUS
23–59 years	24 593/28 888	18 434/24 593
⩾ASCUS	**865/878, 1.16 (1.06–1.27)**	**843/865, 1.30 (1.18–1.43)**
CIN2	71/67, 1.24 (0.89–1.74)	**77/71, 1.45 (1.05–2.00)**
⩾CIN3	**183/151, 1.42 (1.15–1.76)**	**181/183, 1.32 (1.08–1.62)**
CIN treatments	**291/281, 1.22 (1.03–1.43)**	**280/291, 1.28 (1.09–1.51)**
<CIN2	298/318, 1.10 (0.94–1.29)	**275/298, 1.23 (1.05–1.45)**
False positive for ⩾CIN2	611/660, 1.09 (0.98–1.21)	**585/611, 1.28 (1.14–1.43)**
False positive for ⩾CIN3	682/727, 1.10 (0.99–1.22)	**662/682, 1.29 (1.17–1.44)**
PPV for ⩾CIN2	**29%/25%, 1.18 (1.01–1.38)**	31%/29%, 1.04 (0.90–1.20)
PPV for ⩾CIN3	**21%/17%, 1.23 (1.01–1.49)**	21%/21%, 1.01 (0.85–1.22)
23–29 years	2725/2637	1836/2725
⩾ASCUS	**163/110, 1.43 (1.13–1.82)**	**151/163, 1.37 (1.11–1.70)**
CIN2	18/15, 1.16 (0.59–2.30)	**27/18, 2.23 (1.23–4.03)**
⩾CIN3	49/31, 1.53 (0.98–2.39)	**51/49, 1.54 (1.05–2.28)**
CIN treatments	71/52, 1.32 (0.93–1.88)	**80/71, 1.67 (1.22–2.29)**
<CIN2	**43/25, 1.66 (1.02–2.72)**	32/43, 1.10 (0.70–1.74)
False positive for ⩾CIN2	**96/64, 1.45 (1.06–1.98)**	73/96, 1.13 (0.84–1.52)
False positive for ⩾CIN3	**114/79, 1.40 (1.05–1.85)**	100/114, 1.30 (1.00–1.69)
PPV for ⩾CIN2	41%/42%, 0.98 (0.74–1.31)	52%/41%, 1.26 (0.99–1.60)
PPV for ⩾CIN3	30%/28%, 1.07 (0.73–1.56)	34%/30%, 1.12 (0.81–1.55)
30–44 years	11 043/13 342	8541/11 043
⩾ASCUS	**486/438, 1.34 (1.18–1.52)**	**462/486, 1.23 (1.09–1.39)**
CIN2	42/41, 1.24 (0.81–1.90)	42/42, 1.29 (0.84–1.98)
⩾CIN3	**119/96, 1.50 (1.15–1.96)**	110/119, 1.20 (0.92–1.55)
CIN treatments	**183/166, 1.33 (1.08–1.64)**	163/183, 1.15 (0.93–1.42)
<CIN2	**149/141, 1.28 (1.02–1.61)**	131/149, 1.14 (0.90–1.44)
False positive for ⩾CIN2	**325/301, 1.30 (1.12–1.52)**	**310/325, 1.23 (1.06–1.44)**
False positive for ⩾CIN3	**367/342, 1.30 (1.12–1.50)**	**352/367, 1.24 (1.07–1.43)**
PPV for ⩾CIN2	33%/31%, 1.06 (0.88–1.28)	33%/33%, 0.99 (0.83–1.19)
PPV for ⩾CIN3	24%/22%, 1.12 (0.88–1.41)	24%/24%, 0.97 (0.78–1.22)
45–59 years	10 825/12 909	8057/10 825
⩾ASCUS	**216/330, 0.78 (0.66–0.92)**	**230/216, 1.43 (1.19–1.72)**
CIN2	11/11, 1.19 (0.52–2.75)	8/11, 0.98 (0.39–2.43)
⩾CIN3	15/24, 0.75 (0.39–1.42)	20/15, 1.79 (0.92–3.50)
CIN treatments	37/63, 0.70 (0.47–1.05)	37/37, 1.34 (0.85–2.12)
<CIN2	106/152, 0.83 (0.65–1.06)	**112/106, 1.42 (1.09–1.85)**
False positive for ⩾CIN2	**190/295, 0.77 (0.64–0.92)**	**202/190, 1.43 (1.17–1.74)**
False positive for ⩾CIN3	**201/306, 0.78 (0.66–0.93)**	**210/201, 1.40 (1.16–1.70)**
PPV for ⩾CIN2	12%/11%, 1.13 (0.70–1.83)	12%/12%, 1.01 (0.61–1.67)
PPV for ⩾CIN3	7%/7%, 0.95 (0.51–1.78)	9%/7%. 1.25 (0.66–2.38)

Abbreviations: ASCUS = atypical squamous cells of undetermined significance; CIN = cervical intraepithelial neoplasia; LBC = liquid-based cytology; PPV = positive predictive value; triage = in case of ASCUS at age ⩾30 years. Bold signifies significant change comparing the two phases.
[a]Comparison of outcomes, by age group and phase.

Table A7. Laboratory with ThinPrep cytological technology (Odense)[a]		
	Phase 2 vs phase 1	**Phase 3 vs phase 2**
Change in the technology	ThinPrep LBC	ThinPrep Imaging System
Same technology in both phases	Manual reading, cytology triage of ASCUS	ThinPrep LBC, cytology triage of ASCUS
23–59 years	20 921/74 522	33 614/20 921
⩾ASCUS	**536/3423, 0.56 (0.51–0.61)**	**1087/536, 1.26 (1.14–1.40)**
CIN2	**31/183, 0.60 (0.41–0.88)**	**106/31, 2.13 (1.43–3.17)**
⩾CIN3	163/557, 1.04 (0.88–1.24)	249/163, 0.95 (0.78–1.16)
CIN treatments	219/826, 0.94 (0.81–1.10)	389/219, 1.11 (0.94–1.30)
<CIN2	**215/1507, 0.51 (0.44–0.59)**	**433/215, 1.25 (1.07–1.47)**
False positive for ⩾CIN2	**342/2683, 0.45 (0.41–0.51)**	**732/342, 1.33 (1.17–1.51)**
False positive for ⩾CIN3	**373/2866, 0.46 (0.42–0.52)**	**838/373, 1.40 (1.24–1.58)**
PPV for ⩾CIN2	**36%/22%, 1.67 (1.47–1.91)**	33%/36%, 0.90 (0.78–1.04)
PPV for ⩾CIN3	**30%/16%, 1.87 (1.61–2.17)**	**23%/30%, 0.75 (0.64–0.89)**
23–29 years	3075/14 299	5310/3075
⩾ASCUS	208/1066, 0.91 (0.79–1.05)	**435/208, 1.21 (1.03–1.42)**
CIN2	15/93, 0.75 (0.44–1.29)	**61/15, 2.35 (1.34–4.14)**
⩾CIN3	65/250, 1.21 (0.92–1.58)	103/65, 0.92 (0.67–1.25)
CIN treatments	89/373, 1.11 (0.88–1.39)	167/89, 1.09 (0.84–1.40)
<CIN2	63/372, 0.79 (0.60–1.03)	142/63, 1.31 (0.97–1.75)
False positive for ⩾CIN2	**128/723, 0.82 (0.68–0.99)**	271/128, 1.23 (1.00–1.51)
False positive for ⩾CIN3	**143/816, 0.81 (0.69–0.97)**	**332/143, 1.34 (1.11–1.63)**
PPV for ⩾CIN2	38%/32%, 1.20 (0.99–1.45)	38%/38%, 0.98 (0.79–1.21)
PPV for ⩾CIN3	**31%/23%, 1.33 (1.06–1.68)**	**24%/31%, 0.76 (0.58–0.99)**
30–44 years	9342/32 819	14 370/9342
⩾ASCUS	**242/1435, 0.59 (0.52–0.68)**	**472/242, 1.27 (1.09–1.48)**
CIN2	13/73, 0.63 (0.35–1.13)	33/13, 1.65 (0.87–3.13)
⩾CIN3	80/259, 1.09 (0.85–1.39)	132/80, 1.07 (0.81–1.41)
CIN treatments	102/367, 0.98 (0.78–1.21)	188/102, 1.20 (0.94–1.52)
<CIN2	**98/579, 0.59 (0.48–0.74)**	181/98, 1.20 (0.94–1.53)
False positive for ⩾CIN2	**149/1103, 0.47 (0.40–0.56)**	**307/149, 1.34 (1.10–1.63)**
False positive for ⩾CIN3	**162/1176, 0.48 (0.41–0.57)**	**340/162, 1.36 (1.13–1.64)**
PPV for ⩾CIN2	**38%/23%, 1.66 (1.38–2.00)**	35%/38%, 0.91 (0.74–1.11)
PPV for ⩾CIN3	**33%/18%, 1.83 (1.48–2.26)**	28%/33%, 0.85 (0.67–1.07)
45–59 years	8504/27 404	13 934/8504
⩾ASCUS	**86/922, 0.30 (0.24–0.37)**	180/86, 1.28 (0.99–1.65)
CIN2	3/17, 0.57 (0.17–1.94)	12/3, 2.44 (0.69–8.65)
⩾CIN3	18/48, 1.21 (0.70–2.08)	**14/18, 0.47 (0.24–0.95)**
CIN treatments	28/86, 1.05 (0.69–1.61)	34/28, 0.74 (0.45–1.22)
<CIN2	**54/556, 0.31 (0.24–0.41)**	110/54, 1.24 (0.90–1.72)
False positive for ⩾CIN2	**65/857, 0.24 (0.19–0.31)**	**154/65, 1.45 (1.08–1.93)**
False positive for ⩾CIN3	**68/874, 0.25 (0.20–0.32)**	**166/68, 1.49 (1.12–1.97)**
PPV for ⩾CIN2	**24%/7%, 3.46 (2.23–5.38)**	**14%/24%, 0.59 (0.35–0.99)**
PPV for ⩾CIN3	**21%/5%, 4.02 (2.45–6.59)**	**8%/21%, 0.37 (0.19–0.71)**

Abbreviations: ASCUS = atypical squamous cells of undetermined significance; CIN = cervical intraepithelial neoplasia; LBC = liquid-based cytology; PPV = positive predictive value; triage = in case of ASCUS at age ⩾30 years. Bold signifies significant change comparing the two phases.
[a]Comparison of outcomes, by age group and phase.