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Adaptation of CytoProcessor™ for cervical cancer screening of challenging slides

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39 Conflict of interest statement

40 The pathologists were paid standard wages by DATEXIM for their work on the study. No
41 financial advantages or conflicting interests were disclosed.
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53 region through the European Funds for Regional Development.
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Abstract

Background

Current automated cervical cytology screening systems require purchase of a dedicated preparation machine and use of a specific staining protocol. CytoProcessor™ (DATEXIM, Caen, France) is a new automated system, designed to integrate seamlessly into the laboratory's existing workflow. We previously demonstrated the superior performance of CytoProcessor™ for diagnosis of ThinPrep slides compared to the ThinPrep Imaging System (HOLOGIC, Marlborough, MA, USA). Next, we asked if CytoProcessor™ technology can be adapted for use on Novaprep slides.

Methods

Using artificial intelligence, we developed a new algorithm in CytoProcessor™ for the analysis of slides prepared using the NOVAPREP Processor System NPS50 (Novacyt, Vélizy-Villacoublay, France). A representative population of 309 cases was selected from the routine workflow in a public hospital. We compared the diagnoses made using CytoProcessor™ or conventional screening with a microscope. All discordances were resolved by a consensus committee.

Results

The performance of CytoProcessor™ in terms of diagnostic accuracy on Novaprep slides was very similar to that observed previously on ThinPrep slides. Compared to conventional screening, CytoProcessor™ slightly improves diagnostic sensitivity while maintaining a statistically equivalent specificity. Diagnosis was reached 1.6 times faster with CytoProcessor™ compared to using a microscope.

Conclusion

CytoProcessor™ is a robust automated cervical cytology screening system that can be used successfully with samples having very different characteristics. As previously shown,

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3 CytoProcessor™ confers significant gains in processing time and diagnostic precision.
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5 CytoProcessor™ is accessible through a secured internet connection, making remote
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7 diagnosis of Papanicolaou tests possible.
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14 **Keywords**

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16 Digital pathology, artificial intelligence, cervical screening, Papanicolaou test, gynecologic
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Introduction

Cervical cancer causes approximately 275,100 deaths annually.¹ The major causative factor of cervical cancer is infection by the human papillomavirus (HPV), a sexually transmitted virus with an infection rate estimated at 80%.¹ While incidence rate and deaths have progressively declined in developed countries thanks to national deployment of high-cost screening programs and HPV vaccination programs, cervical cancer remains the leading cause of cancer deaths in women in less-developed countries.¹

The Papanicolaou test has proven overwhelmingly successful at preventing mortality from cervical cancer.² A specialized brush is used to collect a cell sample from the cervix, which is then smeared on a slide or suspended in a preservation liquid and sent to a laboratory. There, the cells are stained in order to make apparent the changes in nuclear morphology that can indicate HPV infection. The interpretation of Papanicolaou tests requires a highly trained, specialized workforce of screeners and pathologists. These demands, combined with a lack of training programs and organizational costs make cervical cancer screening unavailable for a great number of women in less-developed countries.¹ Cervical cancer remains the fourth most frequent cancer among women worldwide.³

Two semi-automated systems are currently widely used in Europe and North America: the BD FocalPoint Slide Profiler (Becton, Dickinson and Company, Franklin Lakes, NJ, USA) and the ThinPrep Imaging System (HOLOGIC, Marlborough, MA, USA).⁴ Both of these systems identify abnormal cells based on nuclear staining characteristics, imposing a dedicated sample processor and a fixed staining protocol.^{4,5} One of the major costs for a laboratory in the implementation of these systems is the replacement of the existing sample preparation equipment.⁶

CytoProcessor™ (DATEXIM, Caen, France) was designed to integrate into the laboratory's

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3 existing environment, without requiring the replacement of equipment. The CytoProcessor™
4 platform is intended to incorporate multiple algorithms optimized for cytology images with
5 different characteristics. The flexibility of this solution makes it theoretically possible to use
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CytoProcessor™ with any type of liquid-based preparation and staining protocol.

To verify this hypothesis, we used artificial intelligence to generate a new algorithm adapted to a completely different preparation system and staining protocol from that previously tested.⁷ Our results indicate that CytoProcessor™ is a robust system that can be adapted to challenging samples, such as Novaprep slides.

Materials and Methods

This monocentric, ethics committee-approved, retrospective clinical study compared the performance of conventional microscope screening and CytoProcessor™. This study was conducted in accordance with the Declaration of Helsinki. All subjects who participated gave their informed consent. The study was monitored by the clinical research study coordinator of the Cherbourg Public Hospital. Two reports were established and confirmed that the study was conducted according to protocol.

Diagnostic procedures

Conventional microscope screening consisted in a cytotechnologist first screening the slide completely and marking pertinent cells. A pathologist then performed rapid rescreening of the slide and used the marked cells to provide a medical diagnosis. The pathologist's final diagnosis was used as the microscope diagnosis.

To obtain the CytoProcessor™ diagnosis, a pathologist simply reviewed the first 100 cells selected by CytoProcessor™. The pathologist did not benefit from any prior screening or marks to establish the diagnosis. The pathologist was able to visualize cells in the context of the slide and had the option of screening the entire slide image if desired. The participating pathologists were blinded to all information regarding the original diagnosis.

All data was anonymized to blind the pathologist to the original diagnosis. Cases were presented in random order in CytoProcessor™, along with a print-out of the clinical data and antecedents. To reduce the effects of inter-observer variability, cases were reassigned to the same pathologist having made the microscope diagnosis wherever possible (95% of cases). A washout period of at least 2 months was respected to prevent the investigator from remembering the case.

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3 Diagnoses were categorized using the Bethesda system, the internationally accepted guide
4 for reporting diagnoses of cervical cytology.⁸ The diagnostic categories are as follows for
5 squamous cells, roughly in order of severity: NILM (negative for intraepithelial lesion or
6 malignancy), ASC-US (atypical squamous cells of undetermined significance), LSIL (low-
7 grade squamous intraepithelial lesion), ASC-H (atypical squamous cells - cannot exclude
8 HSIL), HSIL (high-grade squamous intraepithelial lesion), Squamous cell carcinoma. For
9 glandular cells: AGC (atypical glandular cells), AGC neo (atypical glandular cells, favor
10 neoplastic), Adenocarcinoma in situ, Adenocarcinoma.
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22 Training

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24 Four investigators participated in the study, all of whom had 17 or more years experience
25 screening cytology using the conventional method. The investigators were given a one-hour
26 training course in the use of CytoProcessor™ before beginning the study. One investigator
27 had tested a CytoProcessor™ prototype, but none had a routine-setting experience with the
28 system.
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37 Determination of the reference truth diagnosis

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39 When the microscope and CytoProcessor™ diagnoses were concordant, this was
40 considered to be the truth diagnosis. Discordances were resolved by a consensus
41 committee, blinded to the original diagnoses, and discussed until a consensus was agreed
42 upon. The committee was composed of 4 investigators from the hospital. All available data
43 was used by the consensus committee: rescreening of the physical slide, reexamination of
44 the results in CytoProcessor™, and examination of the clinical data/antecedents. The
45 consensus diagnosis served as the truth diagnosis for all subsequent calculations of
46 sensitivity and specificity. Out of 60 cases reviewed, no consensus was possible for 1 case
47 due to the presence of blood, leading it to be excluded from the study.
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Sample preparation

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3 All specimens were prepared using the NOVAPREP Processor System NPS50 (Novacyt,
4 Vélizy-Villacoublay, France) and the Cherbourg hospital's Papanicolaou staining protocol.
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6 The slides were digitized at 40X (resolution 0.28 micrometers/pixel) using a Leica SCN400
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8 slide scanner (Leica Biosystems, Nussloch, Germany).
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13 The specimens were collected in the framework of regular screening (not specifically for the
14 study). In order to ensure that the study would not have an impact on patient care, patients
15 having already received clinical follow-up were selected for participation. The selection was
16 enriched in abnormal cases to provide sufficient statistical measures of sensitivity. The 321
17 patients were addressed a letter explaining the nature of the research and requesting
18 authorization to include their Papanicolaou test(s). Fourteen patients were excluded from the
19 study because they could not be reached by mail or by phone. Another 14 patients sent in
20 the opposition form and were excluded. A total of 293 patients met the inclusion criteria
21 (consent, 18 years or older, slide scanned) and had one or more specimens processed by
22 the hospital, yielding a total of 309 slides available for the study. There were 216 slides used
23 for diagnostic performance assessment and 93 for diagnostic duration measurements.
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39 In order to study the representativity of the sample selection, clinical data were collected for
40 all patients included in the study and for all patients screened between January 2, 2013 and
41 July 19, 2017 (5948 patients). Additionally, we investigated patient characteristics that can
42 generate specific gynecological cytology for randomly selected sets of 100 cases from the
43 routine and study groups. The use of birth control pills, an intrauterine contraceptive device,
44 or an implant is known to generate signs that can be misinterpreted as HPV infection.
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Statistical analyses

The sensitivity of either method was calculated as the number of true positive diagnoses

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3 divided by the number of true positives plus false negatives, using the truth diagnosis as a
4 reference. The specificity was calculated as the proportion of correctly identified negatives
5 among the total negatives as determined by the truth diagnosis.
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11 Statistical significance was estimated by calculating confidence intervals and determining if
12 the intervals overlap. When the intervals did not overlap, the null hypothesis was rejected
13 and it was concluded that a real difference existed. Confidence intervals were determined at
14 95% confidence by adding or subtracting
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$$20 \quad 1.96 \sqrt{\frac{\frac{P}{N} \left(1 - \frac{P}{N}\right)}{N}}$$

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24 from P/N where P is the number of true positives detected and N is the number of true
25 positives plus false negatives. When $N < 30$ the Kaufmann's method was used to better
26 estimate the intervals.⁹ Other statistical tests were performed using R software, version 3.2.3
27 GUI 1.66 Mavericks build (7060).
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33 34 35 Time to diagnosis

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37 Four investigators participated in the timing experiment after having used CytoProcessor™
38 for 1 week. The full diagnostic procedure was timed:
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- 41 1. Review of clinical data and antecedents,
- 42 2. Examination of the slide on the microscope, or the results of CytoProcessor™,
- 43 3. Marking zones of interest on the physical slide, or saving zones of interest using the
44 dedicated tool in CytoProcessor™,
- 45 4. Choosing the diagnostic category and descriptive codes.
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54 The same 93 cases were examined, after a wash-out period of 9 weeks. The same printed
55 sheet showing clinical data was given to the investigators whether they were being timed
56 using the microscope or CytoProcessor™. The same descriptive codes were used.
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Results

Compared to slides prepared using the ThinPrep Processor (HOLOGIC, Marlborough, MA, USA) and stained using the standard HOLOGIC protocol, slides prepared using the NOVAPREP Processor System NPS50 and stained using the Cherbourg hospital protocol differed in several important characteristics (Figure 1). The use of different scanners to acquire the digital images also contributed to differences in the virtual slide images. In Novaprep slides, cell clustering was frequently more pronounced. The Cherbourg hospital staining protocol yields more darkly stained nuclei and magenta-hued superficial cells, as opposed to the orange hue observed with the HOLOGIC staining protocol.

Rejection rate

There were 216 cases presented for diagnosis in CytoProcessor™. The investigator refused to pronounce a diagnosis for 6 cases. This was either due to a problem in the slide preparation such as low cellularity (4 slides), or out-of-focus regions in the image (2 slides). The first is a problem independent of CytoProcessor™. The problem with out-of-focus regions was due to the slide scanner. Overall, this yielded a rejection rate of 1%. Problems with focus can often be resolved by simply cleaning and scanning the slides a second time.

Number of samples

There were 210 cases diagnosed by both methods for which a truth diagnosis was obtained either by concordance or by the consensus committee (Table 1). The selection was enriched in abnormal cases, yielding approximately 73% negative for intraepithelial lesion or malignancy (NILM) and approximately 27% with some degree of abnormality (ASC-US or more severe) according to the truth diagnosis.

Representativity of the data

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3 Age distributions were not significantly different between the study population and the
4 routine population (Welch t-test p-value = 0.99; Figure 2). In addition, every group showing
5 specific gynecological cytology was represented in the study, and none of the differences
6 between the study population and the routine population were statistically significant (Table
7 2). We conclude that the study population was representative of the total population received
8 at the study center.
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18 Sensitivity and Specificity

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20 The clinical consequences of missing an abnormality are more severe than those of
21 mistaking the degree of abnormality. Therefore, the main goal is to successfully detect
22 abnormalities of any category. We first analyzed the results by grouping together all cases
23 having a truth diagnosis of ASC-US or higher (ASC-US+), LSIL or higher (LSIL+), and HSIL
24 and cancer (HSIL+).
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33 CytoProcessor™ is slightly superior to the microscope for detection of ASC-US or more
34 severe (Table 3); however, this improvement is not statistically significant. Likewise,
35 CytoProcessor™ and the microscope showed a statistically equivalent specificity
36 (CytoProcessor™: 0.86, 95% C.I. 0.81 - 0.91; microscope: 0.93, 95% C.I. 0.89 – 0.97).
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43 Table 4 shows the number of abnormalities detected when cases are divided into “normal”
44 and “abnormal” groups. If we consider these simplified groupings of normal and abnormal,
45 we find 22 out of 25 errors (88%) committed with CytoProcessor™ were “false positives,”
46 that is, normal cases diagnosed as abnormal (Table 4). Using the microscope, investigators
47 made 4 false negative errors, whereas they made 3 false negative errors using
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61 For both methods, the false negatives consisted in ASC-US and LSIL cases as determined
62 by the truth diagnosis. No ASC-H, HSIL, or cancer cases were diagnosed as normal by

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3 CytoProcessor™. This can be seen in the confusion matrices in Tables 5 and 6.
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7 Overall, considering that cases with a truth diagnosis of ASC-US or more severe required
8 clinical follow-up, 1.4% of patients would have been missed if the CytoProcessor™ diagnosis
9 had been used for clinical decision-making (3 out of 210). When the microscope diagnosis
10 was used for clinical decision-making, 2% of patients were missed.
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18 Time to diagnosis

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20 We next directly compared the time for a single screener to reach a diagnosis with either
21 method on the same set of slides (Table 7). We found a significant decrease in the duration
22 of diagnosis using CytoProcessor™ compared to the duration using the microscope (Mann-
23 Whitney U test p -value $< 9 \times 10^{-6}$) (Table 7). On average, for the same cases, diagnosis with
24 CytoProcessor™ is 1 minute faster. Assuming that 5% of slides will be reviewed by a
25 pathologist, the laboratory would save 1.75 hours of worker time every 100 slides on the
26 diagnosis step alone.
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37 The elimination of slide handling steps in the CytoProcessor™ workflow saves a further
38 10.85 minutes every 100 slides (transferring slides to trays, transferring trays to screeners
39 and pathologists, matching slides with data sheets, distributing slides to screeners; data from
40 7). The only additional manual step required in the CytoProcessor™ workflow compared to
41 the conventional workflow is loading the scanner, which requires approximately 4.5 minutes
42 per 100 slides. If we subtract this from the time saved by eliminating slide handling, we
43 obtain a savings of 6.32 minutes every 100 slides. Therefore, using CytoProcessor™ instead
44 of a microscope saves a total of 1.86 hours every 100 slides. A laboratory processing
45 100,000 slides per year with a 6-hour working day would thus save 310 days per year.
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Discussion

CytoProcessor™ is designed as a flexible system using artificial intelligence that can integrate into the existing laboratory workflow. We previously demonstrated the performance of CytoProcessor™ for analysis of ThinPrep slides stained with the standard HOLOGIC protocol.⁷ Here, we have shown that the system can be easily adapted to challenging Novaprep slides, a completely different staining protocol, and a different slide scanner.

In this study, the performance of CytoProcessor™ in terms of diagnostic accuracy was statistically equivalent to that of the conventional method. The risk of a false-negative diagnosis was remarkably low (1.4%), despite the challenges of Novaprep slides. This was nearly identical to that observed in our previous study (1.5% risk of false-negative⁷). In the context of the routine workflow, this performance was obtained with the added benefit of approximately 1.6 times faster diagnosis.

As explained in the methods section, there were significant biases against CytoProcessor™. The investigators had no prior experience using CytoProcessor™ in a routine setting, and only a one-hour training session. They all had at least 17 years experience at the consultant level using a microscope. The microscope diagnosis was established by a screener and pathologist working sequentially to identify any potential abnormalities. In contrast, only one pathologist made the diagnosis with CytoProcessor™, without the help of marks by a previous screener. Although the sensitivity of CytoProcessor™ reported here is already slightly higher than that of the conventional method, we consider it as a baseline. Likewise, the specificity is expected to improve with experience, as already demonstrated in our first study.⁷

The conventional microscope workflow is simple and straightforward; yet, there are many manual steps where time is wasted. By eliminating slide handling steps and converting to a

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3 digital system, highly trained screeners and pathologists can spend more time on
4 diagnosis.¹⁰ Instead of ordering and laying out slides in trays and then searching manually
5 for the right slide, the screeners simply scan a barcode to jump to the slide image in the
6 CytoProcessor™ interface. One of the most remarkable results of this study is the speed
7 with which diagnosis was reached using CytoProcessor™. Allowing CytoProcessor™ to
8 perform the tedious screening step saves a full minute per slide on average, while achieving
9 equivalent diagnostic accuracy.
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20 The flexibility of CytoProcessor™ allows it to be integrated simply and rapidly in the
21 laboratory workflow, without needing to purchase dedicated slide preparation equipment or
22 change the current staining protocol. This reduces the user training period to a strict
23 minimum, since the slides still have the same appearance. CytoProcessor™ also provides
24 flexibility in terms of site organization. The digital nature of the system allows slides to be
25 prepared and scanned at one site, while screeners access the images and make diagnosis
26 at multiple remote sites. This novel design facilitates the organization of resources to
27 optimize processing.
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39 In conclusion, CytoProcessor™ is a robust automated cervical cancer screening system that
40 can be successfully adapted to different conditions. The time savings gained through the
41 simple CytoProcessor™ workflow permit more slides to be processed without an increase in
42 the workforce, increasing the feasibility of large-scale screening in resource-poor settings.
43 The use of virtual slide images greatly accelerates data transmission, and avoids the risk of
44 breaking fragile glass slides during transport. The fully digital design of CytoProcessor™
45 allows remote diagnosis through a secured internet connection. Together, these advantages
46 improve working conditions for screeners and the quality of healthcare for patients.
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Figure 1. Comparison of an example of a ThinPrep slide used in our previous study (top), and a Novaprep slide, the focus of the current study (bottom). Note the differences in hues, cell dispersion and staining intensity.

Figure 2. Distribution of patient age in years at the time of screening for the study population (black) and the whole population screened between January 2, 2013 and July 19, 2017 (5948 patients; gray).

Table 1. Proportions of diagnostic categories in the dataset as determined using the truth diagnosis. There were no true ASC-H or glandular abnormalities.

Category	Number of cases	Percentage of total
NILM	153	71%
ASC-US	10	5%
LSIL	34	16%
HSIL	12	6%
Squamous cell carcinoma	1	0.5%
Unsatisfactory for evaluation	6	3%

Table 2. Proportions of patients recorded as having the characteristic in 100 randomly selected cases from the study population and the routine population. Differences are determined to be statistically significant at 95% confidence if the intervals do not overlap.

Characteristic	Routine population (95% confidence intervals)	Study population (95% confidence intervals)	Statistically significant
Intrauterine device	0.13 (0.06-0.20)	0.25 (0.17-0.33)	No
Birth control pills	0.03 (0.00-0.06)	0.11 (0.05-0.17)	No
Implant	0.02 (0.00-0.05)	0.02 (0.00-0.05)	No
Menopause	0.09 (0.03-0.15)	0.05 (0.01-0.09)	No
Pregnant or	0.04 (0.00-0.08)	0.06 (0.01-0.11)	No

postpartum			
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Table 3. Sensitivity of detection of grouped Bethesda diagnostic categories comparing CytoProcessor™ and the microscope using the truth diagnosis as a reference. Differences are determined to be statistically significant at 95% confidence if the intervals do not overlap.

Bethesda category	Number of diagnoses	Sensitivity microscope (95% confidence intervals)	Sensitivity CytoProcessor™ (95% confidence intervals)	Statistically significant
ASC-US +	57	0.93 (0.86-1.00)	0.95 (0.89-1.00)	No
LSIL +	47	0.91 (0.83-0.99)	0.89 (0.80-0.98)	No
HSIL +	13	0.69 (0.38-0.91)	0.85 (0.55-0.97)	No
Cancer	1	0.00	1.00	No

Table 4. Confusion matrices comparing CytoProcessor™ (CP) and the microscope (MS) where cases are determined to be “normal” (negative for intraepithelial lesion or malignancy) or “abnormal” (ASC-US+) using the truth diagnosis as a reference.

		Truth		
		Normal	Abnormal	Total
CP	Normal	131	3	134
	Abnormal	22	54	76
	Total	153	57	210

		Truth		
		Normal	Abnormal	Total
MS	Normal	142	4	146

	Abnormal	11	53	64
	Total	153	57	210

Table 5. Confusion matrix for CytoProcessor™ diagnoses (CP) compared with truth diagnoses. The diagonal represents diagnoses exactly matching the truth.

		Truth						
		Normal	ASC-US	LSIL	ASC-H	HSIL	Cancer	Total
CP	Normal	131	2	1	0	0	0	134
	ASC-US	8	3	3	0	1	0	15
	LSIL	11	3	30	0	0	0	44
	ASC-H	2	1	0	0	2	0	5
	HSIL	1	1	0	0	9	0	11
	Cancer	0	0	0	0	0	1	1
	Total	153	10	34	0	12	1	210

Table 6. Confusion matrix for the microscope diagnoses (MS) compared with truth diagnoses. The diagonal represents diagnoses exactly matching the truth.

		Truth							
		Normal	ASC-US	LSIL	ASC-H	HSIL	Cancer	AGC	Total
MS	Normal	142	3	1	0	0	0	0	146
	ASC-US	5	4	3	0	0	0	0	12

LSIL	0	0	26	0	2	0	0	28
ASC-H	1	0	1	0	1	1	0	4
HSIL	4	3	3	0	9	0	0	19
Cancer	0	0	0	0	0	0	0	0
AGC	1	0	0	0	0	0	0	1
Total	153	10	34	0	12	1	0	210

Table 7. Average duration of diagnosis on the same set of 93 cases.

Microscope	CytoProcessor™
2 min 43 seconds	1 min 39 seconds

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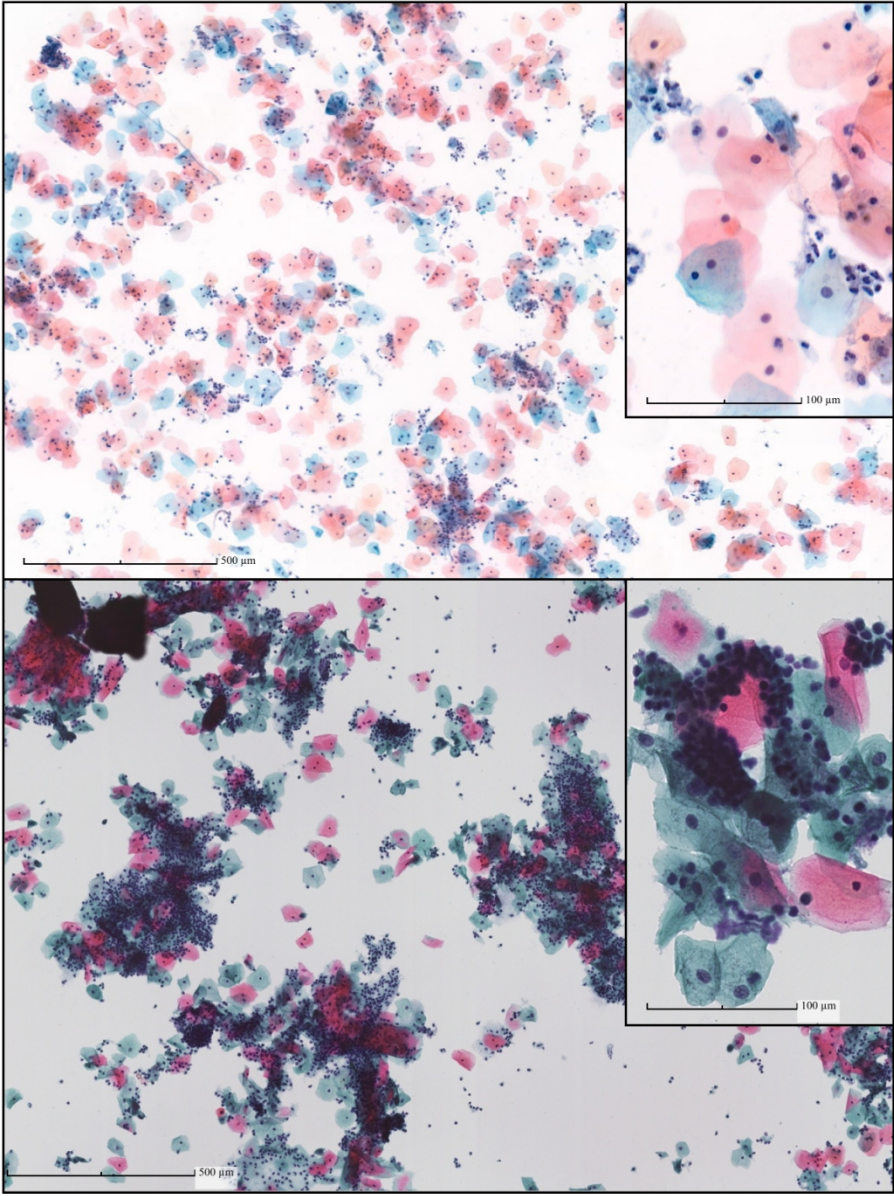


Figure 1. Comparison of an example of a ThinPrep slide used in our previous study (top), and a Novaprep slide, the focus of the current study (bottom). Note the differences in hues, cell dispersion and staining intensity.

101x135mm (300 x 300 DPI)

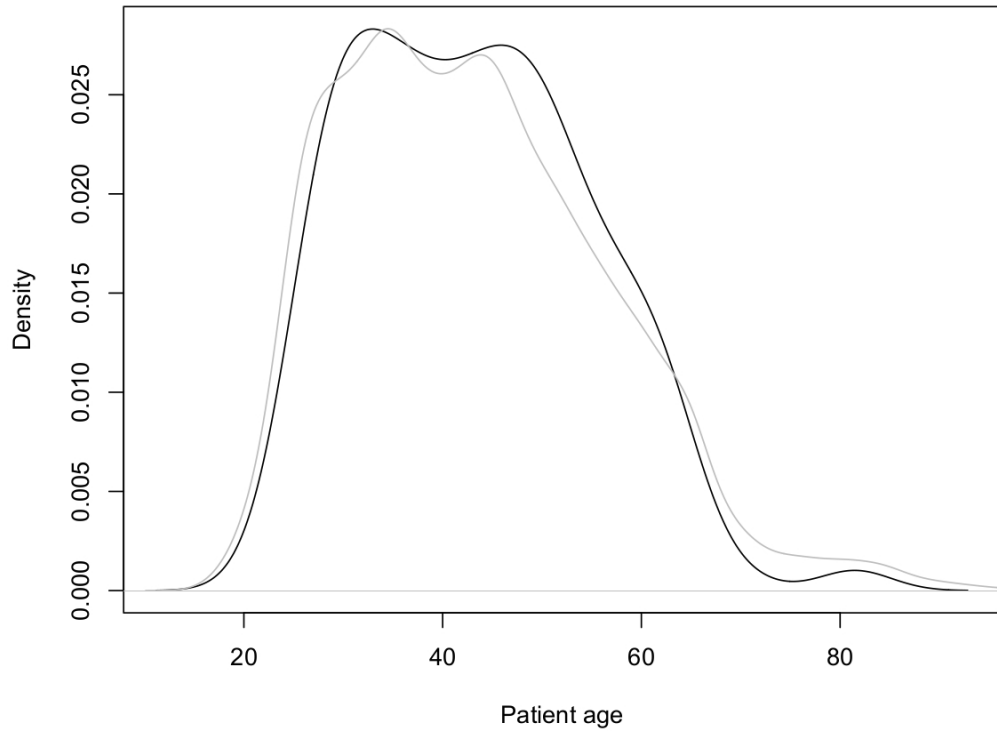


Figure 2. Distribution of patient age in years at the time of screening for the study population (black) and the whole population screened between January 2, 2013 and July 19, 2017 (5948 patients; gray).

95x70mm (300 x 300 DPI)