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Analytical and diagnostic quality of HPV self-samples for cervical cancer screening after biobank storage

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Keywords

Biobanking

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HPV self-sampling

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Cancer audit

Abbreviations

HPV: human papillomavirus

HR-HPV: high risk human papillomavirus (oncogenic HPV types)

CIN: Cervical intraepithelial neoplasia

Ct-value: Cycle threshold value

HBB: Human beta-globin

RBGB: Bio- and Genome Bank, Denmark

DScB: Danish Screening Biobank

Abstract (non-structured)

Self-sampling is a robust alternative to clinician collected sampling when screening for cervical cancer and is increasingly being implemented in national screening programs. After analysis, the remaining sample can be preserved for audits and for the development and validation of new technologies. However, evidence regarding the long-term stability of biobanked self-samples is limited.

This study evaluated the performance of biobanked clinical self-samples, stored at −20°C with subsequent transfer to −80 °C for long term storage at the Danish Screening Biobank at Hvidovre Hospital.

The original analysis using the polymerase chain reaction (PCR) BD Onclarity HPV assay on the BD Viper LT platform, was repeated after 3, 5 and 7 years of biobanking. Sample degradation was evaluated using numerical internal control and HPV cycle threshold values (Ct-values) and diagnostic output (HPV positive/negative).

Sample degradation was registered as a non-significant minor increase in internal control and HPV Ct-values with a corresponding shift in diagnostic output for samples with Ct-values close to diagnostic cut-off. Degradation was uniform and independent of storage time, which is likely attributable to single events such as freezing and/or thawing.

In conclusion, current biobanking procedures for self-samples at the Danish Screening Biobank are suitable for both audit and research purposes.

Introduction

Persistent infection with Oncogenic or High-risk HPV (HR-HPV) is the predominant cause of cervical cancer and PCR-based HPV testing has been established as the standard cervical cancer screening test(1, 2). In the Danish cervical cancer screening program, all women aged 30-64 years are offered HPV-based screening without direct expense for the women(3, 4). Samples can be collected either by a clinician or as self-samples. Self-sampling is becoming increasingly popular among underscreened populations by circumventing the practical, cultural, and psychological barriers associated with pelvic examination(5-11). In Denmark, HPV self-sampling is currently limited to screening non-attenders but other countries like the Netherlands, Sweden, and Australia have implemented HPV self-sampling in their standard screening program.

After HPV analysis, it is possible to biobank the remaining sample material. Reanalysis of stored samples may be required for audits when screening fails and screened women develop cancer, allowing the screening institution to better identify the root causes of diagnostic failure. Sample preservation also enables supplementary testing and biobanking preserves high-quality clinical samples, providing a reference for validation of new diagnostic technologies(12). However, these benefits can only be utilized if sample integrity is maintained over time. Deviations in biobanking procedures such as variations in manual handling or storage temperatures can lead to sample degradation and heterogeneity, and biobanking protocols must therefore be validated and standardized.

Since implementation of HPV self-sampling in the Capital Region of Denmark, all analyzed samples have been biobanked in the Danish Screening Biobank (DScB) which is part of the Bio- and Genome Bank Denmark (RBGB). RBGB is a national biobank infrastructure governed by the 5 Danish regional healthcare authorities together with Danish hospital administrations and is coordinated on a national level by the RBGB secretariat located at Herlev Hospital. The RBGB database maintains a central register, detailing biobanked samples from 14 medical specialties, including rheumatological, cancer and blood biobanks. Samples are biobanked locally or at centralized hospital biobanks in accordance with RBGB defined storage criteria and with standardized documentation regarding preanalytical and analytical processes which is registered in the RBGB database. (13).

The quality of biobanked HPV self-samples is currently undocumented in the literature. As a first of its kind, it is therefore important to document the analytical and diagnostic quality of biobanked HPV self-samples and their quality for audit, reanalysis, and validation of experimental diagnostic technologies. The purpose of this study is thus to examine the analytical and diagnostic quality of self-collected cervical cancer screening samples over time when biobanked for 3, 5 and 7 years.

Results

Storage effect measured on internal control (HBB)

Changes in internal control Ct-values, were used as a proxy measure for sample degradation. Mean differences were calculated as row-vise subtraction of original – study cycle threshold values (Ct-values), and the mean was calculated from the differences. With samples biobanked for 3 years, the mean difference was 1.12 95 % CI [1.07,1.17], for 5 years 1.04 95 % CI [1.0,1.08], and for 7 years the mean difference of 1.29 95 % CI [1.25,1.33]. All three differences were statistically significant ($p<0.0001$) (Figure 1). HPV Ct-values were all below the 3 Ct-values that were defined as success criteria before initiating the study.

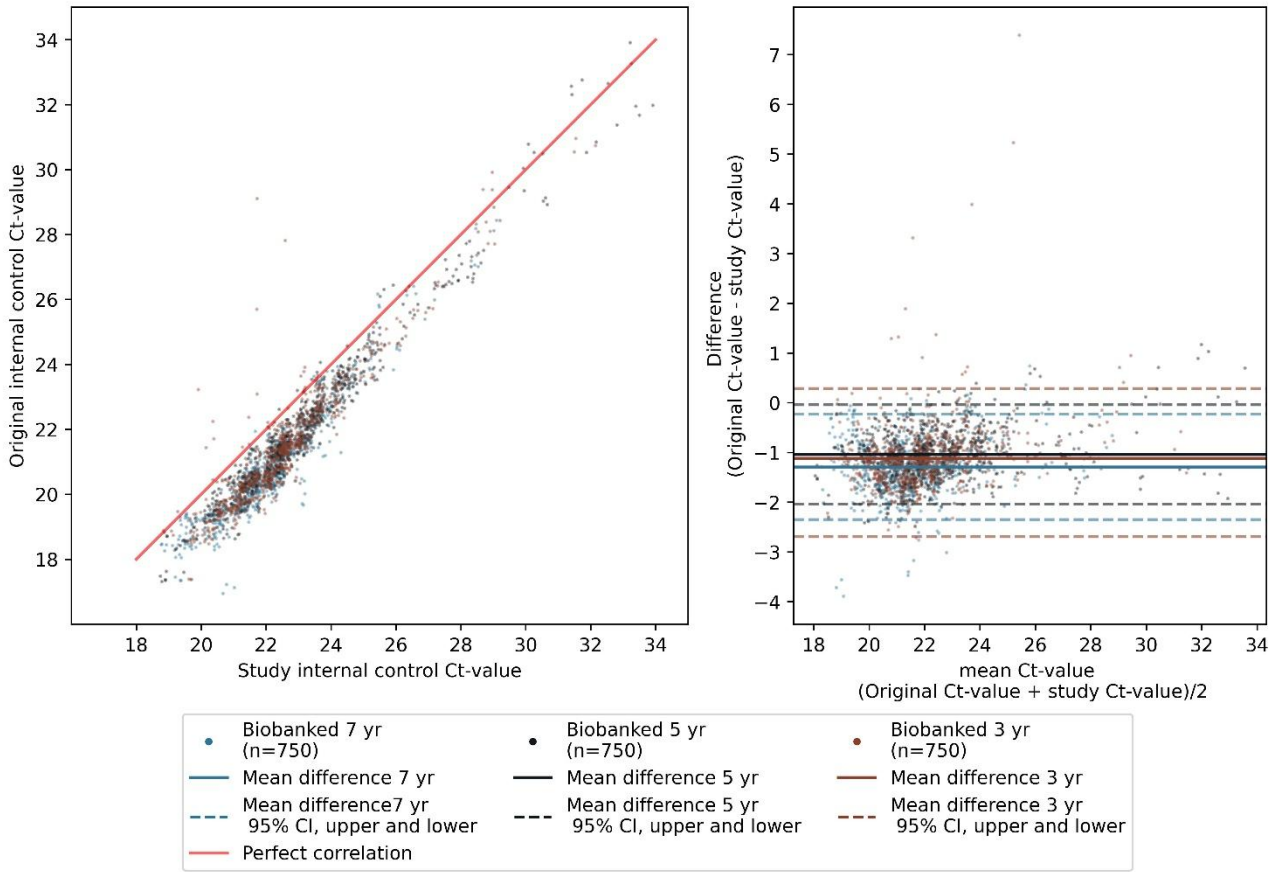

Figure 1: Left: Original Ct-value on y-axis and study Ct-value on x axis. Central red line shows perfect correlation, when Ct-values of original and study analysis are identical.

Right: Bland-Altmann plot with difference in Ct-values on y-axis and mean Ct-values ((original Ct-value + study Ct-value)/2) on x-axis.

Storage effect measured on HPV Ct-value

All paired HPV Ct-values were isolated and mean differences were calculated. If either the original or study analysis were negative, both were excluded in order not to skew the analysis. For HPV Ct-values, samples stored for 3 years (n=108) had a mean difference of 0.79, 95 % CI [0.62,0.96], for 5 years (n=123) mean difference was 0.94, 95 % CI [0.75,1.13] and for 7 years (n=125) mean difference was 1.03, 95 % CI [0.83,1.23], none of the differences were statistically significant (p= 0.16, 0.15, 0.32) (Figure 2).

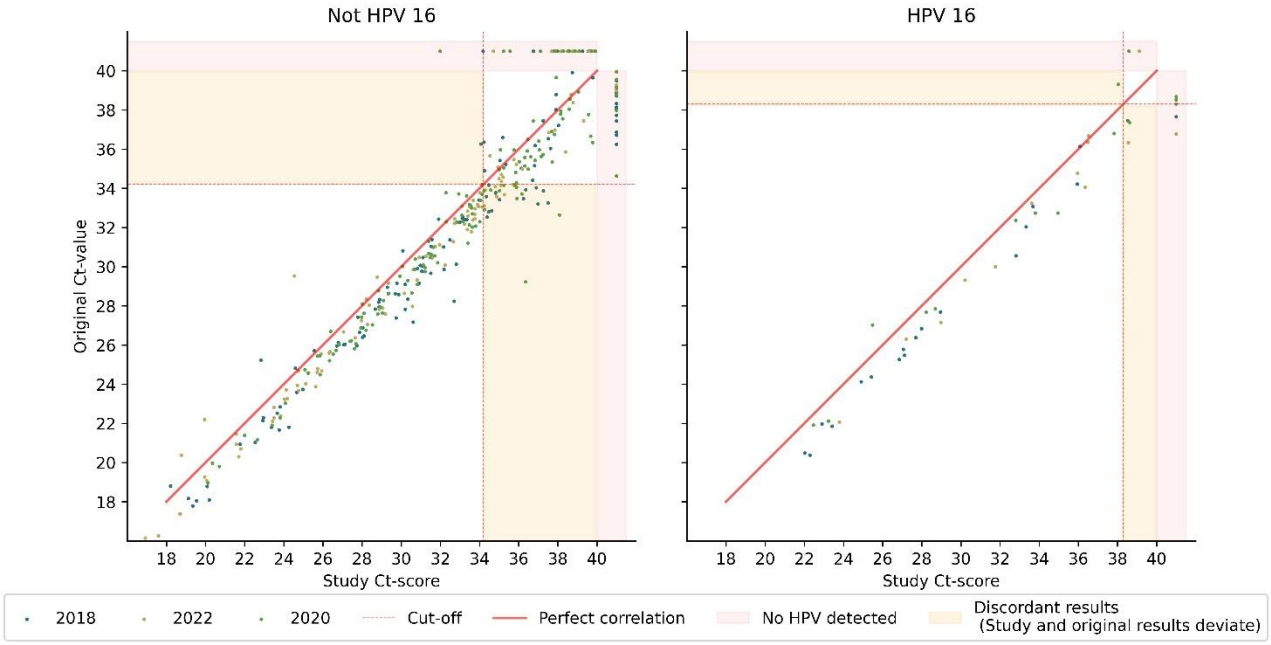

Figure 2: Scatterplots showing Ct-scores of all paired tests in the study, that contained a HPV-Ct value, note that tests that only contained HPV-Ct-values above the Cut-off, were diagnosed as HPV negative, but also that some women were infected with several HPV types. y-axis: original Ct-value, x-axis: Study Ct-value. Red squares indicate Ct-values of 0, i.e. No HPV was detected. Yellow squares indicate discordant analysis, where HPV was detected, but above the diagnostic cut-off.

Reproducibility of original diagnostic results

Reproducibility of the original diagnostic result was evaluated by comparing the categorical output (HPV positive/negative) of samples stored for 3, 5, and 7 years (n = 250 per group). A modest decline in sample quality was seen with increasing storage duration (Table 1). For samples stored 3 years, overall agreement was 0.98 (95% CI, 0.96–1.0), meeting the pretrial criterion for "Good" performance; sensitivity was 0.95 (95% CI, 0.87–0.99), specificity 1.0 (95% CI, 0.98–1.0), positive predictive value 1.0 (95% CI, 0.95–1.0), and negative predictive value 0.98 (95% CI, 0.94–0.99). For samples stored 5 and 7 years, overall agreement

was 0.96 (95% CI, 0.92–0.98) at both time points, meeting the criterion for "Acceptable" performance; sensitivity, specificity, positive predictive value, and negative predictive value were correspondingly 0.87 (95% CI, 0.77–0.93), 0.99 (95% CI, 0.97–1.0), 0.98 (95% CI, 0.92–1.0), and 0.95 (95% CI, 0.90–0.97) at both durations. Overall, reproducibility outcome remained within pretrial acceptance criteria at all three time points.

Four paired samples, biobanked for 3 years, were categorically discordant, all four with a Ct-value increase below 2 Ct. The categorical differences were not statistically significant (p=0.125). Eleven paired samples, biobanked for 5 years, were categorically discordant, with a total of 11 paired HPV scores, one was decreased, the remaining were increased Ct-values, and 11 of these with a difference below 2 Ct values. The categorical differences were statistically significant (p=0.01). Eleven paired samples biobanked for 7 years were categorically discordant, with a total of 13 paired HPV scores. Twelve of these were due to increases, and one due to a decrease. With 6 samples, the difference was below 2 Ct-values. The categorical differences were statistically significant (p=0.01).

	Years biobanked		
	3	5	7
Total	250	250	250
+/+	71	65	65
-/-	175	174	174
+/-	4	10	10
-/+	0	1	1
Overall agreement [95% CI]	0.98 [0.96,1.0]	0.96 [0.92,0.98]	0.96 [0.92,0.98]
Evaluation defined pretrial	Good	Acceptable	Acceptable
Sensitivity [95% CI]	0.95 [0.87,0.99]	0.87 [0.77,0.93]	0.87 [0.77,0.93]
Specificity [95% CI]	1.0 [0.98,1.0]	0.99 [0.97,1.0]	0.99 [0.97,1.0]
Positive predictive value [95% CI]	1.0 [0.95,1.0]	0.98 [0.92,1.0]	0.98 [0.92,1.0]
Negative predictive value [95% CI]	0.98 [0.94,0.99]	0.95 [0.9,0.97]	0.95 [0.9,0.97]

Table 1: Reproducibility of original diagnostic results

Discussion

In this study we have compared the diagnostic reproducibility and evaluated shifts in internal control Ct-values of cervical cancer screening self-samples after 3, 5 and 7 years of biobanking.

The consistent shift of approximately 1 Ct-value in internal control Ct-values was independent of storage duration and suggests that the reduction in analytical performance is caused by single events, such as

freezing–thawing rather than a time-dependent, sequential decline in sample quality. Our findings are in line with other studies, that also describe minor increases in Ct-values over time (14, 15).

Regarding the diagnostic reproducibility, overall agreement exceeded 90% in all cohorts, with a modest reduction in sensitivity after 5 and 7 years of biobanking (Table 1). Most discordant test results were due to minor shifts within HPV Ct-values where the original Ct-value was close to manufacturer defined cutoff. All predefined success criteria were fulfilled, supporting the robustness of the current biobanking procedures for HPV self-samples at the DScB and confirm their suitability for both audit and research purposes.

Comparing our results to current literature, we identified only two studies detailing PCR based performance on biobanked material from cervical screening. A Danish study examined DNA stability of clinician collected samples in ThinPrep medium and stored at -18 °C and the study reported similar high agreements as here (16). In a Swedish study, samples were stored for 2 – 6 months at -20 °C with a reported 84 % agreement when using the Aptima mRNA assay, and 87% agreement using QIAamp DNA minikit(17). When comparing results from both studies with results obtained in our study, we conclude our results to be similar, however, with a slightly higher overall agreement.

Implementation of biobanking is not without costs, it can be labor intensive, which can be partially mitigated with the recent development of automated platforms and requires robust information management system, and skilled staff to operate(18). Additionally, biobanking requires freezers and indoor storage areas with climate control to house them, and finally, freezers consume energy. The recommended storage temperature is -80°C but with increased government focus on climate sustainability in the Danish hospital sector, recommended temperatures are being increased with defined aim of halving climate emission by 2035, and climate neutrality by 2050 in accordance with EU objectives(19, 20). Concretely RBGB biobanking temperature have been increased from -80°C to-70 and -60°C with ~30% decrease in energy consumption for long-term sample storage(21). A limitation of our study is that we cannot account for the time distribution of samples stored at -20°C and -80°C, with a proportion of samples having been stored only at -20°C, with our documented minimal sample degradation.

The efficiency of HPV vaccination has been documented when given before sexual debut and is associated with minimal side effects(22). However, the effect decreases with prior HPV exposure, meaning that late vaccinated and unvaccinated population groups will likely require continued screening. Cervical cancer screening programs, and the associated benefits of biobanking are therefore expected to be relevant for several decades with a gradually diminishing patient group(23).

Screening biobanks are unique, because they contain chronologically ordered samples from the site of carcinogenesis which allows us to retrogradely examine the incremental disease progression in women who develop cancer. Via the RGBG infrastructure and civil registration number, it can also be linked to samples from other organs as well as patient information from clinical databases thereby providing insights that may be applicable to other HPV dependent cancers such as penile, throat, and anal cancer(12, 24).

There is an ongoing debate regarding the parity of self-samples relative to clinician collected samples, with a comprehensive meta study that documents its parity when detecting CIN2+ (2, 25). Self-sampling is included as a popular standard screening offer in both Holland, Sweden and Australia (26-28). Self-sampling is a cheaper and less invasive alternative to clinician collected sampling, and with our study we document the added option of biobanking.

In conclusion, the current biobanking procedures for HPV self-samples, stored for up to 7 years, at the Screening Biobank at Hvidovre Hospital are suitable for both audit and research purposes.

Method

Study design and cohort

In 2025, a total of 750 biobanked self-samples, 250 stored for 3, 5 and 7 years respectively, were retrieved from the Danish screening biobank at Hvidovre Hospital, and reanalyzed. All samples were clinical screening samples, from screening eligible women residing in the Capitol Region of Denmark. To ensure sufficient sensitivity estimates, the cohort was enriched with 30% HPV positive samples relative to a screening population of approximately 6% (5, 29). Samples from 2018 were originally analyzed between 03.01 – 15.02, 2020 between 07.01 – 28-08 and 2022 between 16.03 – 07.07. Samples were retrieved from the biobank from May 2025 to February 2026. Retrieved samples were thawed and vortexed for 20 seconds and 1 ml sample was transferred from the biobank container to an empty BD tube. Samples were pre-heated and analyzed using the BD Onclarity HPV assay on the BD Viper LT system, which reports HR-HPV type 16, 18, 45, 31, 51 and 52 individually, and “HR-HPV 33 & 58” , “HR-HPV 56 & 59 & 66” and “HR-HPV 35 & 39 & 68” in groups(30). To limit degradation, no more than 5 days passed between thawing and analysis. Original diagnostic results, including internal control and HPV Ct-scores were retrieved and compared with results from the repeated analysis.

Original sample processing and analysis

All self-samples were collected using the Evalyn Brush (Rovers, Oss, The Netherlands) as previously described (5). Upon reception, the Evalyn brush head was removed and transferred to a BD Onclarity™ HPV

Self Collection Diluent Tubes (Waters Advanced Diagnostics, Sparks, MD) containing 3.0 ml CBD medium in compliance with standard operating procedure.

With samples received after February 2020, both biobanked and analyzed material was preheated but with samples older than February 2020 only the analyzed material was preheated. With each analysis, The BD Viper LT uses 0.8 ml sample material for DNA extraction, leaving approximately 2.0 ml to be stored in the clinical biobank (excepting errors). Finally, the sample was stored in a refrigerator until 30 samples were collected and transferred in batch to the BD Viper™ LT for analysis using the BD Onclarity™ HPV Assay. At most, 5 days passed between reception and analysis.

Biobanking protocol for HPV self-samples since 2017

After original analysis, the remaining cervical brush diluent medium (CBD medium, Waters Advanced Diagnostics, Sparks, MD, 2 ml) was manually transferred to a labelled Eppendorf tube and stored in a -20°C freezer with its location (ID, container, row and column number) stored in a local database. The transfer was usually done the subsequent workday, in case of combined weekend and holiday, a maximum of 4 days passed. After analysis batches of samples were registered in RBGB and stored in a local biobank freezer at -80°C.

Cutoff-values

The diagnostic output (HPV positive/HPV negative) was based on manufacturer set cutoff values of ≤38.3 for HPV 16 and ≤34.2 for the remaining HR-HPV types. If at least one HR-HPV CT-value was less than the cutoff value, a diagnosis of HR-HPV positive was reported. Because cutoff values were reevaluated in 2018, the diagnostic output(HPV positive/negative) of 2018 samples were reevaluated using contemporary cutoff values(30).

Statistical analysis

Original and study mean internal control Ct-values was used as a proxy measure for DNA stability. The original analysis was used as reference.

Categorical data (Positive/Negative) and overall agreement, sensitivity, specificity positive and negative predictive value were reported, confidence intervals were calculated using the Clopper-Pearson method. Because the number of discordant results were below 25, statistical significance was calculated using McNemar's exact test.

Each analysis outputs 3 internal control Human beta-globin(HBB) Ct-values. Original and study internal control Ct-values were separately merged, and significance was evaluated using T-tests. The pretrial

defined success criteria were set as a difference in mean internal control Ct-score less than 3 Ct and an overall diagnostic agreement of 0.90-0.94 was evaluated as “acceptable”, and > 0.95 was evaluated as “good”.

Ct-values of discordant HPV results are illustrated in a point-plot, significance was evaluated using T-tests. All calculations and statistics were done using python v.3.13.7, matplotlib v.3.10.6 (32), pandas v.2.3.3(33), seaborn v.0.13.2 (34), statsmodels v. 0.14.5(35) and scipy v.1.16.3 (36) packages in a jupyter lab notebook Version v.4.4.9.

1. Koliopoulos G, Nyaga VN, Santesso N, Bryant A, Martin-Hirsch PPL, Mustafa RA, et al. Cytology versus HPV testing for cervical cancer screening in the general population. Cochrane Database of Systematic Reviews. 2017(8).
2. Arbyn M, Smith SB, Temin S, Sultana F, Castle P. Detecting cervical precancer and reaching underscreened women by using HPV testing on self samples: updated meta-analyses. Bmj. 2018;363:k4823.
3. Das M. WHO launches strategy to accelerate elimination of cervical cancer. Lancet Oncol. 2021;22(1):20-1.
4. IARC. Cervical cancer screening volume 182022.
5. Ejegod DM, Pedersen H, Pedersen BT, Serizawa R, Bonde J. Operational experiences from the general implementation of HPV self-sampling to Danish screening non-attenders. Prev Med. 2022;160:107096.
6. Pedersen BT, Sonne SB, Pedersen H, Andreasen EK, Serizawa R, Ejegod DM, et al. Participation and relative cost of attendance by direct-mail compared to opt-in invitation strategy for HPV self-sampling targeting cervical screening non-attenders: A large-scale, randomized, pragmatic study. Int J Cancer. 2025;156(8):1594-605.
7. De Pauw H, Ducancelle A, Arbyn M, Pivert A, Le Duc Banaszuk AS, Noyelle J, et al. Women's perceptions and preferences toward HPV self-sampling in France: A questionnaire within the French CapU4 Trial. J Infect Public Health. 2025;18(8):102809.
8. Morgan K, Azzani M, Khaing SL, Wong YL, Su TT. Acceptability of Women Self-Sampling versus Clinician-Collected Samples for HPV DNA Testing: A Systematic Review. J Low Genit Tract Dis. 2019;23(3):193-9.
9. Tranberg M, Bech BH, Blaakær J, Jensen JS, Svanholm H, Andersen B. HPV self-sampling in cervical cancer screening: the effect of different invitation strategies in various socioeconomic groups - a randomized controlled trial. Clin Epidemiol. 2018;10:1027-36.
10. Burger EA, Sy S, Nygård M, Kim JJ. The Cost-Effectiveness of Cervical Self-Sampling to Improve Routine Cervical Cancer Screening: The Importance of Respondent Screening History and Compliance. Cancer Epidemiol Biomarkers Prev. 2017;26(1):95-103.
11. Pretsch PK, Spees LP, Brewer NT, Hudgens MG, Sanusi B, Rohner E, et al. Effect of HPV self-collection kits on cervical cancer screening uptake among under-screened women from low-income US backgrounds (MBMT-3): a phase 3, open-label, randomised controlled trial. Lancet Public Health. 2023;8(6):e411-e21.
12. Arbyn M, Van Veen EB, Andersson K, Bogers J, Boulet G, Bergeron C, et al. Cervical cytology biobanking in Europe. Int J Biol Markers. 2010;25(3):117-25.
13. RBGB. Guiding Principles, PIXI 2025. Available from: https://www.rbgb.dk/wp-content/uploads/2025/09/A8_en.-Guiding-Principles-PIXI-1.pdf.

14. Dzung A, Cheng PF, Stoffel C, Tastanova A, Turko P, Levesque MP, et al. Prolonged Unfrozen Storage and Repeated Freeze-Thawing of SARS-CoV-2 Patient Samples Have Minor Effects on SARS-CoV-2 Detectability by RT-PCR. J Mol Diagn. 2021;23(6):691-7.
15. Yu K, Xing J, Zhang J, Zhao R, Zhang Y, Zhao L. Effect of multiple cycles of freeze-thawing on the RNA quality of lung cancer tissues. Cell Tissue Bank. 2017;18(3):433-40.
16. Ørnskov D, Waldstrøm M, Thomsen LT, Munk C, Kjær SK. Quality Control of Biospecimens in a Danish Clinical Cytology Biobank. Biopreserv Biobank. 2023;21(2):184-90.
17. Larsson GL, Karlsson MG, Helenius G. HPV testing of biobanked liquid-based cytology - a validation study. Int J Biol Markers. 2016;31(2):e218-23.
18. Perskvist N, Norman I, Eklund C, Litton JE, Dillner J. The Swedish cervical cytology biobank: sample handling and storage process. Biopreserv Biobank. 2013;11(1):19-24.
19. Regioner D. En fællesregional strategi for grønne hospitaler. 2023.
20. Shabihkhani M, Lucey GM, Wei B, Mareninov S, Lou JJ, Vinters HV, et al. The procurement, storage, and quality assurance of frozen blood and tissue biospecimens in pathology, biorepository, and biobank settings. Clin Biochem. 2014;47(4-5):258-66.
21. Madsen C, Høgdall E. ULT freezer performance and dual-temperature storage in a modern biobank: preserving sample integrity during transition. Journal of Laboratory Medicine. 2026;50:10-20.
22. Henschke N, Bergman H, Buckley BS, Crosbie EJ, Dwan K, Golder SP, et al. Effects of human papillomavirus (HPV) vaccination programmes on community rates of HPV-related disease and harms from vaccination. Cochrane Database of Systematic Reviews. 2025(11).
23. Nonboe MH, Napolitano GM, Kann C, Andersen B, Bennetsen MH, Christiansen S, et al. Screening outcome of HPV-vaccinated women: Data from the Danish Trial23 cohort study. PLoS One. 2024;19(6):e0306044.
24. Annaratone L, De Palma G, Bonizzi G, Sapino A, Botti G, Berrino E, et al. Basic principles of biobanking: from biological samples to precision medicine for patients. Virchows Arch. 2021;479(2):233-46.
25. Ransohoff DF, Feinstein AR. Problems of spectrum and bias in evaluating the efficacy of diagnostic tests. N Engl J Med. 1978;299(17):926-30.
26. Monitor Dutch cervical cancer screening programme 2024. 2025.
27. (NKCx) NKfC. Förebyggande av livmoderhalscancer i Sverige Verksamhetsberättelse och Årsrapport 2025 med data till och med 2024 2025.
28. National Cervical Screening Program monitoring report 2025. 2025.
29. Cancerscreening SAfCo. Dansk Kvalitetsdatabase for Livmoderhalskræftscreening Årsrapport 2024. 2025.
30. FDA. Summary of safety and effectieness data(SSED) of BD Onclarity HPV Assay 2018. Available from: https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160037B.pdf.
31. Deeks JJ, Takwoingi Y, Macaskill P, Bossuyt PM. Understanding test accuracy measures. Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy2023. p. 53-72.
32. Hunter JD. Matplotlib: A 2D Graphics Environment. Computing in Science & Engineering. 2007;9(3):90-5.
33. McKinney W. Data Structures for Statistical Computing in Python2010. 56-61 p.
34. Waskom M. seaborn: statistical data visualization. Journal of Open Source Software. 2021;6:3021.
35. Seabold S, Perktold J. Statsmodels: Econometric and Statistical Modeling with Python. Proceedings of the 9th Python in Science Conference. 2010;2010.
36. Virtanen P, Gommers R, Oliphant TE, Haberland M, Reddy T, Cournapeau D, et al. SciPy 1.0: fundamental algorithms for scientific computing in Python. Nature Methods. 2020;17(3):261-72.

Author contributions/Credit statement

Conceptualization: AA, EH, JB

Methodology: AA, EH, JB

Software: AA

Validation: AA, HP

Formal analysis: AA

Investigation: AA, HP

Resources: AA, HP

Data curation: AA, HP

Writing – original draft: AA

Writing – review and editing: AA, EH, JB

Visualization: AA

Supervision: EH, JB

Project administration: AA, EH, JB

Funding acquisition: JB, EH

Ethics declarations

The study was approved as a quality assurance study by AHH-Hvidovre Hospital Institutional Review Board, j. nr: 15937456. All methods were performed in accordance with the relevant guidelines and regulations. The study approval explicitly states that informed consent is not required from women whose samples are included in the study and this is in accordance with Danish law regarding quality assurance studies. As per Danish regulatory requirement, retrieved samples were cross-checked against the Danish Tissue Utilization Register (Sundhedsdatastyrelsen), a national registry recording citizens who have opted out of having their biological material used in research, including scientific studies.

Data availability statement

Study data is archived at AHH-Hvidovre Hospital, aggregated data can be made available by contacting the corresponding author.

Competing interests

AA, HP: The authors declare no conflict of interest.

JBO: Institution has received research funding and/or consumables at reduced price or for free to support research from BD Diagnostics (US) and Seegene (South Korea). JBO has received honoraria for lectures from BD Diagnostics, Copan and Seegene.

EH: Institution has received research funding and/or consumables at reduced price or for free to support research from ThermoFisher, Roche, Astra Zeneca (Sweden) Merck (USA) and Servier (France).

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