Journal of the American Society of Cytopathology (2025) xx, 1–9

Available online at www.sciencedirect.com

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journal homepage: www.jascyto.org/

Diagnostic performance of the hologic genius digital diagnostics system for low-grade squamous intraepithelial lesion (LSIL) ThinPrep papanicolaou tests

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Received 10 December 2024; received in revised form 10 January 2025; accepted 12 January 2025

KEYWORDS
Digital pathology;
Low grade squamous intraepithelial lesion;
ThinPrep Papanicolaou test;
Artificial intelligence;
Cervical cancer screening

Introduction Advancements in digital imaging technology for Papanicolaou test slides, combined with artificial intelligence are driving the development and adoption of innovative computer-assisted screening methods for cervical cancer within the cytology community. Our study aimed to assess the performance of the Hologic Genius Digital Diagnostic System (HGDDS) in the interpretation of low-grade squamous intraepithelial lesions (LSIL) in ThinPrep Papanicolaou slides.

Method As part of a validation study performed with 890 ThinPrep Papanicolaou slides using the HGDDS, a subset of 146 LSIL cases were included in this study. Performance characteristics for the detection of cervical intraepithelial neoplasia (CIN) and interobserver variability among 3 cytopathologists were assessed.

Results On evaluation of the consensus results of the 3 cytopathologists, of the 146 LSIL Papanicolaou cases, 60.3% were interpreted as LSIL with the HGDDS. The remainder were interpreted as ASCUS

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https://doi.org/10.1016/j.jasc.2025.01.003

(26%), ASC-H (10.3%), HSIL (2.7%), and NILM (0.7%). The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for detecting CIN1+ lesions in the ASCUS + category with the HGDDS were 100%, 25%, 97.9%, and 100%, respectively. The sensitivity, specificity, PPV, and NPV for the detection of CIN1+ lesions in the LSIL + category with the HGDDS were 74.7%, 75%, 99.1%, and 7.7%, respectively. Kendall's W coefficient was 0.792, indicating strong agreement among participating pathologists.

Conclusions Our study demonstrated that ThinPrep Papanicolaou tests with LSIL could be interpreted with strong agreement among pathologists and with good performance indicators when utilizing the HGDDS.

Introduction

Cervical cancer is the fourth most common cancer globally, with around 660,000 new cases and 350,000 reported deaths in 2022, with the highest incidence and mortality seen in middle- and low-income countries.[1] Persistent human papillomavirus (HPV) infection is the causative factor of this cancer type, with early detection and treatment proving to be the mainstays of management of these patients.[1] Utilizing Papanicolaou test screening for cervical cancer has helped reduce the incidence of this disease by 80% in the United States.[2,3] Subsequently, the overwhelming number of Papanicolaou smears requiring manual screening limited by a diminishing cytology workforce was, and still remains, a strong factor driving the emergence of computer-assisted automated screening systems.[4] The advent of liquid-based cytology (LBC) solutions in the 1990s, followed by the arrival of the first US Food and Drug Administration (FDA) approved automated LBC screening devices such as the ThinPrep Imaging system in the 2000s heralded a new era in gynecologic cytopathology practice.[4]

Despite advances related to improving Papanicolaou test evaluation culminating in commercial automated systems, there has been a need for additional changes in the practice of cytopathology in order to mitigate various issues encountered by cytology laboratories in today's climate. The foremost among these problems is the dire staffing shortage, especially for highly skilled cytologists in low-resource and/or rural settings, and owing to decreasing enrollment in cytotechnology schools in the United States.[5,6] Other challenges routinely encountered with Papanicolaou test screening include inaccurate results (eg, false positives and negatives), significant intra- and interobserver variability with subjective manual screening, increasing workload, increased turnaround times, centralization of cytology services, litigation risk, mental and physical fatigue and health (ergonomic) issues faced by personnel screening Papanicolaou test slides.[7-12] Advances in computational biology, whole-slide imaging, and artificial intelligence (AI) have the potential to collectively help improve automated Papanicolaou test screening systems that in turn can alleviate some of the aforementioned challenges.[7,8,13,14] Moreover, digital cytopathology provides additional benefits such as remote sign-out capabilities, virtual education, reduced need for transport and physical slide storage, as well as easy archiving and digital storage of images.[15]

The Hologic Genius Digital Diagnostic System (HGDDS) for Papanicolaou test screening is an advanced commercially available platform that offers AI-assisted screening of digitized ThinPrep Papanicolaou test slides that has recently been cleared by FDA. The HGDDS consists of a digital imager (scanner), cervical AI algorithm, image management system with server, and review station. The HGDDS utilizes a volumetric imaging technique where a single pass of a ThinPrep glass slide through the system simultaneously acquires images in up to 14 planes, after which advanced image processing merges the pixels in optimal focus from multiple planes into a single layer. The Genius Cervical AI algorithm objectively analyzes all of the cells and objects in the digitized slide and identifies concerning cells, even those in clusters, as well as certain microorganisms that are clinically relevant. The deep learning–based algorithm then selects the most relevant diagnostic images (up to 60 static tiled or thumbnail images), and presents them in an explainable gallery format for review by the cytologist end-user.[16,17] When deploying new technology such as the HGDSS into the cytology laboratory for routine clinical care, it is imperative to ensure that this new system produces accurate and reliable results, thus guaranteeing the safety and quality of patient test results. For regulatory purposes, such as maintaining laboratory accreditation, it also behooves cytology laboratories to validate new systems such as the HGDDS before adopting it into clinical practice. Toward achieving this goal, we validated the HGDDS with archival ThinPrep Papanicolaou tests. The current study focuses on the performance characteristics of the HGDDS specific to LSIL Papanicolaou test cases, which represented a subset of our main validation study.[14] This study also highlights the interobserver variability observed among cytopathologists interacting with this AI-based system.

Materials and methods

This study was conducted after receiving approval from the institutional review board of the University of Pittsburgh.

Archived ThinPrep Papanicolaou test cytology cases from January 2023 to August 2023 were reviewed and those cases with a prior diagnosis according to The Bethesda System for Reporting Cervical Cytology (TBS) of low-grade squamous intraepithelial lesion (LSIL), atypical squamous cells of unknown significance (ASCUS), and negative for intraepithelial lesion or malignancy (NILM) were included. Additionally, archival ThinPrep Papanicolaou test cases from January 2021 to August 2023 with an interpretation of high-grade squamous intraepithelial lesion (HSIL); atypical squamous cells, high-grade not excluded (ASC-H); and atypical glandular cells (AGS) were also included. The study cohort only included abnormal Papanicolaou test cases that had a histologic follow-up result within 6 months of diagnosis after the Papanicolaou diagnosis.

A total of 890 Papanicolaou test cases including 146 cases of LSIL (16%) were included for the HGDDS validation study. At the outset of this study, 3 experienced cytopathologists and 3 cytologists who were recruited to participate in this study underwent training with the HGDDS. Hologic personnel were present on site and conducted a 2-day training session for this group of 6 participants. The HGDDS was installed on premises at our institution, designated for research purposes only. In order to simulate our cytology laboratory clinical workflow, the cytologists reviewed enrolled cases initially, with each cytologist reviewing one third of the cases. Their results were available to the 3 cytopathologists who then reviewed all of the cases individually. The cytologists and cytopathologists looked at the panel images as displayed by the Genius system as well as the whole slide imaging wherever required to arrive at an accurate diagnosis. Except for the age of the patient, no other clinical data nor HPV status was provided regarding enrolled patients.

The sensitivity of the detection of LSIL cases by the 3 participating pathologists was calculated. Performance characteristics of the HGDDS such as sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for the detection of CIN1 + and CIN 2+ lesions were evaluated for a 95% CI. The consistency of the interpretations among the 3 cytopathologists was assessed by the Kendall's W coefficient from the non-parametric test (for the K-relevant samples). Generally, Kendall's W $>$ 0.4 indicates good correlation.

Papanicolaou test cytology categories relevant to this sub-study

ASCUS + included all cases with at least a diagnosis of ASCUS and above including ASC-H and AGC.

LSIL + included cases with a diagnosis of at least LSIL and above lesions.

Histologic categories relevant to this sub-study

CIN1+ included all cases with at least a diagnosis of CIN1 and above lesions.

CIN 2/3 included all cases with a diagnosis of CIN2, CIN3, HSIL/CIN2-3, HSIL/CIN2/3.

Results

The average age of patients included in this LSIL study was 40.1 years (range 23-71 years). Out of the 146 LSIL Papanicolaou test cases, 61.6%, 56.8%, and 58.9% of the cases were diagnosed as LSIL by pathologist A (PA), pathologist B (PB) and pathologist C (PC) with the HGDDS. Further, 4.8%, 2.1%, and 2.1% of these cases were interpreted as NILM by PA, PB, and PC, respectively. Very few of these LSIL cases were interpreted as HSIL cases (2.1% by PA, 2.7% by PB, and 3.4% by PC). The remainder of the diagnoses were divided between ASC-US and ASC-H cases, with more cases being called ASC-US than ASC-H (Table 1; Figs. 1-4). The Kendall W coefficient was 0.792, indicating that the interpretation of LSIL Papanicolaou test cytology among the three pathologists has strong agreement.

In cases with discrepant findings among the 3 pathologists, the final diagnosis was deemed to be the one that was concordant between 2 of the 3 cytopathologists (Figs. 5 and 6). Of the original 146 LSIL cases, the final HGDDS diagnosis was LSIL in 60.3%, ASC-US in 26%, ASC-H in 10.3%, HSIL in 2.7%, and NILM in 0.7% (Table 1). On correlation of this final diagnosis of LSIL Papanicolaou

Table 1 The interpretation of 146 LSIL Papanicolaou tests using the Genius system among 3 pathologists.

TBS	Pathologist A		Pathologist B		Pathologist C		Final dx	
	Cases, no.	%	Cases, no.	%	Cases, no.	%	Cases, no.	%
LSIL	90	61.6	83	56.8	86	58.9	88	60.3
ASC-US	33	22.6	39	26.7	35	24.0	38	26.0
ASC-H	13	8.9	17	11.6	17	11.6	15	10.3
HSIL	3	2.1	4	2.7	5	3.4	4	2.7
NILM	7	4.8	3	2.1	3	2.1	1	0.7

Abbreviations: TBS, The Bethesda System; NILM, negative for intraepithelial lesion and malignancy; ASC-US, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; ASC-H, atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion.

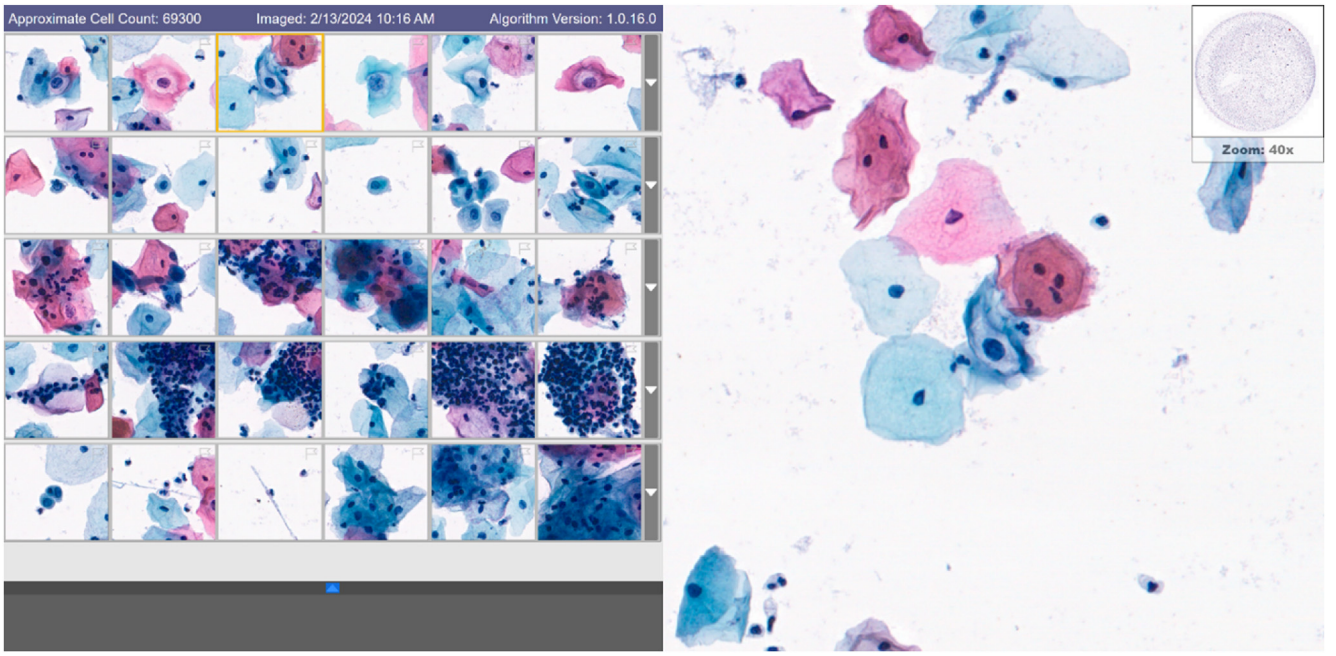

Figure 1 Screenshot from HGDDS showing a 23-year-old patient, interpreted as LSIL by all 3 pathologists. The final HGDDS diagnosis was LSIL, with CIN1 on follow-up biopsy.

cases by HGDDS (88 cases) with histologic follow-up, 78.4% of the cases demonstrated CIN1 lesions, 20.5% had CIN 2/3 lesions, and 1 case was interpreted as benign. Of the 38 cases diagnosed as ASCUS with the HGDDS, 86.8% had a CIN 1 diagnosis, 5.3% had a benign diagnosis, and 7.9% had a CIN2/3 diagnosis on follow-up biopsy. Of the 15 cases diagnosed as ASC-H with HGDDS, 80% were called CIN1 and 20% were called CIN2/3 on histologic follow-up. Out of the 4 cases diagnosed as HSIL with HGDDS, 2 showed CIN1 and the

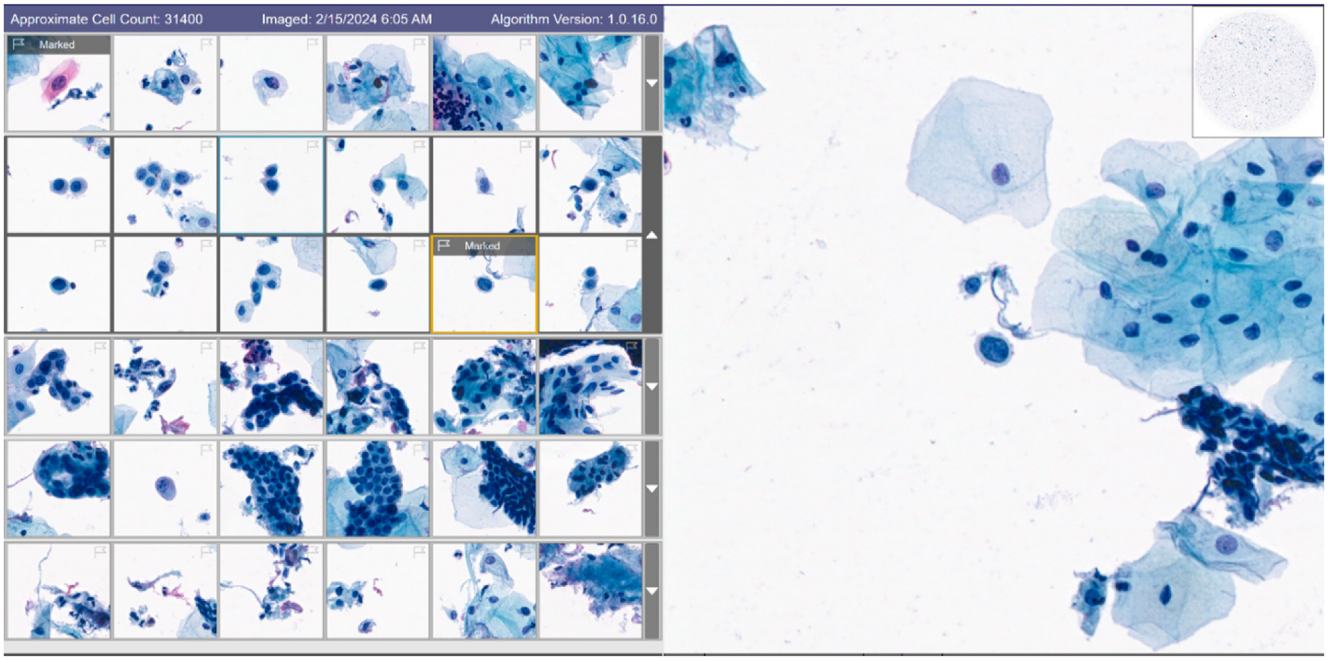

Figure 2 Screenshot from HGDDS showing a 49-year-old patient, interpreted as ASC-H by all 3 pathologists. The final HGDDS diagnosis was ASC-H, with CIN2 on the follow-up biopsy.

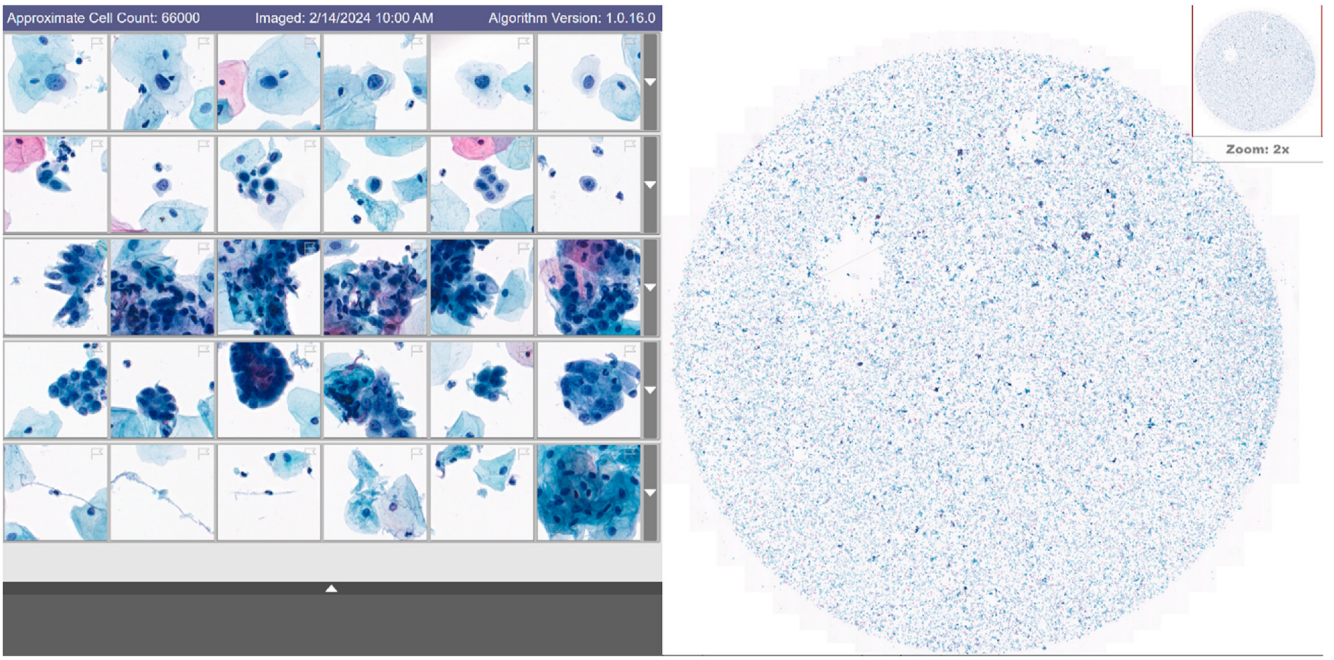

Figure 3 Screenshot from HGDDS showing a 40-year-old patient, interpreted as HSIL by all 3 pathologists. The final HGDDS diagnosis was HSIL, with CIN2 on the follow-up biopsy.

other 2 demonstrated CIN2/3. The one negative Papanicolaou test case had a benign follow-up biopsy (Table 2).

The final cytologic diagnosis with HGDDS system showed 100% sensitivity, 25% specificity, 97.9% PPV, and 100% NPV for the detection of CIN1 and above (CIN1+) lesions when ASCUS + Papanicolaou slides (n = 145) were considered. On examining the LSIL + cohort group (n = 107), the cytologic diagnosis with HGDDS showed

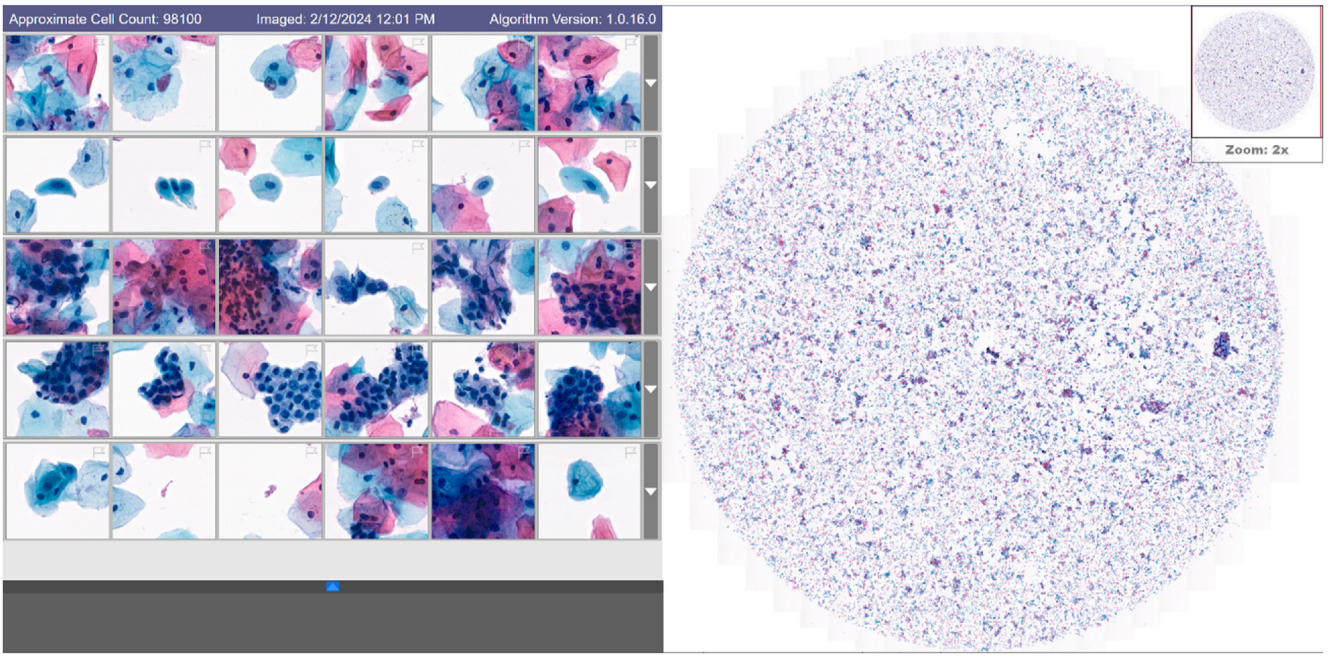

Figure 4 Screenshot from HGDDS showing a 45-year-old patient, interpreted as NILM by all 3 pathologists. The final HGDDS diagnosis was NILM, with benign diagnosis on the follow-up biopsy.

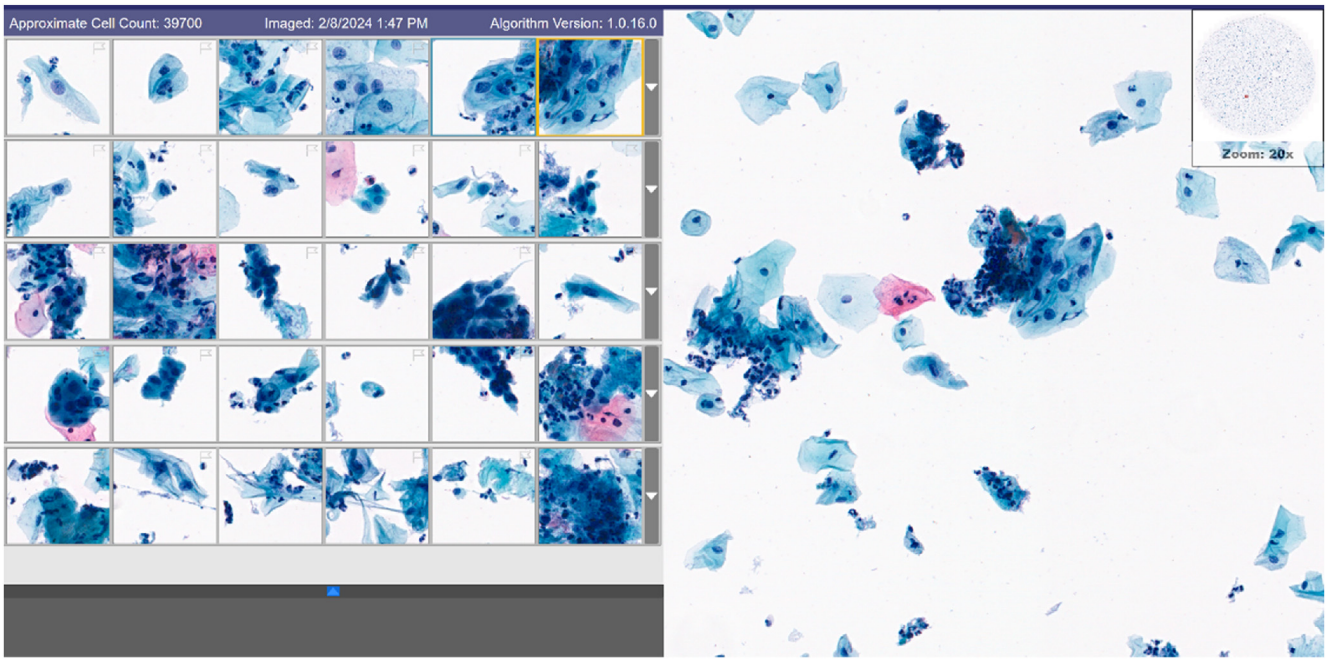

Figure 5 Screenshot from HGDDS showing a 30-year-old patient, interpreted as ASC-US by 2 pathologists and LSIL by 1 pathologist. The final HGDDS diagnosis was ASC-US, with CIN1 on follow-up biopsy.

74.7% sensitivity, 75% specificity, PPV 99.1%, and NPV 7.7% for detecting CIN1+ lesions (Table 3).

The sensitivity for the detection of CIN2/3+ lesions on follow-up biopsy was 100% if ASCUS + cohort of 145 cases diagnosed with the HGDDS were considered. The specificity, PPV, and NPV for this group was 0.8%, 17.9% and 100%, respectively. For the LSIL + group diagnosed using the HGDDS, the sensitivity, specificity, PPV, and NPV for the detection of CIN2/3+ lesions on follow-up biopsy were 88.5%, 30%, 21.5%, and 92.3%, respectively (Table 4).

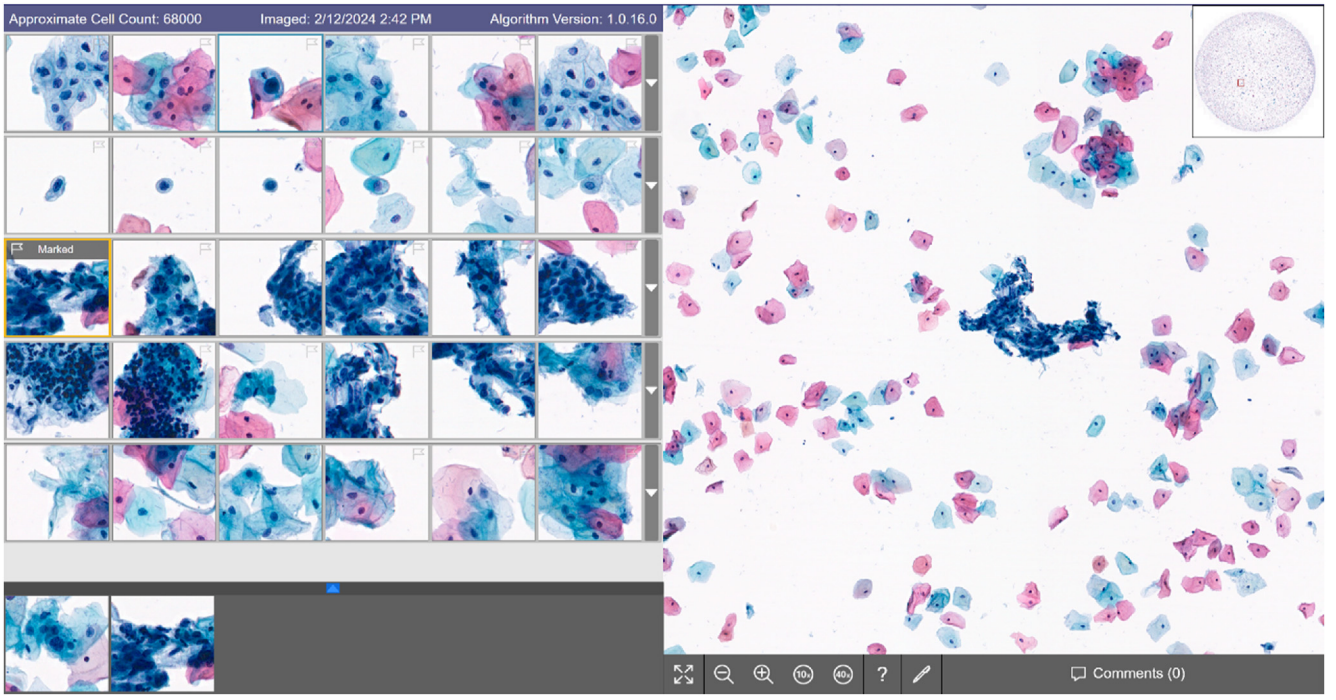

Figure 6 Screenshot from HGDDS showing a 38-year-old patient, interpreted as ASC-US by 2 pathologists and LSIL by 1 pathologist. The final HGDDS diagnosis was ASC-US, with negative for dysplasia on follow-up biopsy.

Table 2 Histology follow-up diagnoses correlated with Papanicolaou Test final diagnosis rendered with the Genius system.

TBS	F-U cases, no.	Benign, n (%)	CIN1, n (%)	CIN2/3, n (%)
LSIL	88	1 (1.1)	69 (78.4)	18 (20.5)
ASC-US	38	2 (5.3)	33 (86.8)	3 (7.9)
ASC-H	15	0 (0)	12 (80.0)	3 (20.0)
HSIL	4	0 (0)	2 (50.0)	2 (50.0)
NILM	1	1 (100.0)	0 (0)	0 (0)
Total	146	4 (2.7)	116 (79.5)	26 (17.8)

Abbreviations: TBS, The Bethesda System; NILM, negative for intra-epithelial lesion and malignancy; ASC-US, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; ASC-H, atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion, CIN1, cervical intraepithelial neoplasia 1; CIN2/3, cervical intraepithelial neoplasia 2/3.

Discussion

Technologic advances in the field of digital pathology have enabled the emergence of high throughput scanners with the ability to acquire high-resolution images from cytology slides with excellent image quality and that are in focus, as well as the application of AI.[15] Whole slide imaging—based cytology screening systems with AI algorithms have been developed and are available commercially to analyze digitized LBC slides.[18] Notably, these digital cytology systems have the potential to mitigate staffing shortages of skilled cytologists, and enable remote screening. Further, indirect benefits of these newer digital cytology platforms include easy storage and compilation of cases with image portability that support teleconsultation, virtual education, and AI-based research.[7,8]

The diagnosis of LSIL on a Papanicolaou test is based on specific microscopic cytological findings (eg, nuclear enlargement, hyperchromasia, perinuclear halo, koilocytes). In general, the diagnosis of LSIL on LBC Papanicolaou tests is straightforward and yields high accuracy. Nevertheless, LSIL interpretation is subject to false positives, false negatives, and inter-reader variability.[19] ThinPrep Papanicolaou test cases with a diagnosis of LSIL that have significantly few abnormal cells (<50) usually perform poorly.[10,20,21] For this reason, we believed it was important to evaluate the performance of the HGDDS when screening ThinPrep Papanicolaou test cases with LSIL. This is, to the best of our knowledge, the first US-based study of its kind evaluating the performance of the HGDDS for screening LSIL Papanicolaou tests in comparison with manual ThinPrep Papanicolaou test review.

In this study, a total of 146 cases of ThinPrep Papanicolaou tests that were originally interpreted as LSIL were thus included in an 890-case cohort evaluated by 3 cytopathologists utilizing the HGDDS. LSIL was the most common interpretation, ranging from 56.8% to 61.6% for all 3 pathologists. The second most common interpretation was ASC-US, ranging from 22.6% to 26.7% for all 3 pathologists. The Kendall W coefficient in our study was 0.792, indicating strong agreement between the participating cytopathologists. The concordance for LSIL lesions was found to be better than that of HSIL lesions studied with the HGDDS in the same institution by the same 3 cytopathologists (0.722).[14]

In our study, 26% of LSIL cases were downgraded to ASC-US with HGDDS interpretation. The main reason likely was lack of clinical information and unavailability of HPV results in the information provided to the study participants. Nineteen of 146 (13.0%) LSIL cases were upgraded to ASC-H or HSIL with the HGDDS. Of these 19 cases, 5 cases (26.3%) were found to have CIN2/3 in histologic follow-up, indicating possible increased capacity of distinguishing HSIL from LSIL by the HGDDS. Whether this indicates a superior performance by the Genius system in terms of diagnosing HSIL cases or this is the result of missed HSIL diagnosis in the original Papanicolaou test diagnosis is open to interpretation. In our opinion, the very low numbers of such cases precludes arriving at a conclusion at this point of time. Additional large-scale studies comparing the performance of the Genius system with the original system utilizing cases with missed interpretations would be beneficial to answer this interesting question.

The PPV for CIN2/3 and CIN1+ was 21.5%, and 99.1% with HGDDS, which is higher when compared with the

Table 3 Performance characteristics for detection of CIN1+ lesions.

Genius system	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV (95% CI)	NPV (95% CI)
ASCUS+ (145)	100 (97.4-100)	25.0 (0.6-80.6)	97.9 (96.4-98.8)	100 (2.5-100)
LSIL+ (107)	74.7 (66.7-81.6)	75.0 (19.4-99.4)	99.1 (95.1-99.8)	7.7 (4.2-13.6)

Abbreviations: ASC-US+, atypical squamous cells of undetermined significance and above; LSIL+, low-grade squamous intraepithelial lesion and above; CIN1+, cervical intraepithelial neoplasia 1 and above, 95% CI, 95% confidence interval; PPV, positive predict value; NPV, negative predict value.

Table 4 Performance characteristics for detection of CIN2/3 lesions.

Genius system	Sensitivity, %	Specificity, %	PPV (95% CI)	NPV (95% CI)
ASCUS+ (145)	100 (86.8-100)	0.8 (0.02-4.6)	17.9 (17.7-18.2)	100 (2.5-100)
LSIL+ (107)	88.5 (69.9-97.6)	30.0 (22.0-39.0)	21.5 (18.6-24.7)	92.3 (80.0-97.3)

Abbreviations: ASC-US+, atypical squamous cells of undetermined significance and above; LSIL+, low-grade squamous intraepithelial lesion and above; CIN2/3, cervical intraepithelial neoplasia 2/3, 95% CI, 95% confidence interval; PPV, positive predict value; NPV, negative predict value.

original Papanicolaou test interpretation. Additionally, on analyzing the performance characteristics of the HGDDS for detection of CIN1+ and CIN 2/3+ lesions, it was found that the sensitivity and NPV for the ASCUS + Papanicolaou test category was 100%. Also, the HGDDS had high sensitivity for the detection of CIN1+ and CIN2/3+ lesions in the LSIL + category.

One of the strengths of our study was that we compared the HGDDS-aided diagnoses with subsequent biopsy proven tissue diagnosis.[22,23] Additionally, the LSIL cases that were included in this study were randomly mixed in the study population of a larger validation study set at the time of review (data forthcoming in a separate paper). Furthermore, this study was purely based on cytomorphology since other pertinent patient information such as HPV status, HPV genotyping results, past clinical history, prior Papanicolaou diagnosis, and so forth, was not shared with the reviewers. Although 60% of the cases were called frank LSIL when utilizing the HGDDS, the remainder were classified into other Bethesda categories. These results are somewhat comparable to the recent Ikenberg study, where results of digital cytology interpretation with the Hologic system were compared to the results with the ThinPrep Imaging system.[22] Their study showed a complete match in 86.56% of reviewed cases, with 12.79% of cases showing a minor discrepancy and 0.65% of cases showing a major discrepancy. However, the study conditions were different with personnel involved in the Ikenberg study, having more experience reviewing digital slides as compared to our team who had limited interaction with the digital system.[24]

Our study exhibited very high sensitivity for the detection for CIN1+ and CIN2/3+ lesions when considering ASCUS+ and LSIL + cases, with 75% specificity for detecting CIN1+ lesions in the LSIL + category. However, the other TBS categories showed lower specificities. These results could be attributed to misclassification of cases into other categories because of dealing with an unfamiliar digital system with minimal training. Additionally, nuanced morphologic changes due to review of 2D images derived from 3D clusters could be one of the reasons for this finding. Despite the challenges encountered with an unfamiliar digital environment with minimal training, learning curve, and dearth of metadata that would normally be available during clinical sign out, our results are encouraging with good performance indices for the detection of LSIL lesions with the HGDDS.

Conclusion

The current study demonstrated that the HGDDS has good performance characteristics and strong interobserver variability for the detection of LSIL lesions in ThinPrep Papanicolaou test slides. More experience with this new digital system and additional training are essential before successful application and integration of this AI-based digital system into clinical practice.

Conflict of interest disclosures

Sarah Harrington is an employee of Hologic Inc.

All other authors have no conflict of interest.

CRediT authorship contribution statement

Lakshmi Harinath: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Esther Elishaev:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis. **Yuhong Ye:** Investigation, Formal analysis. **Jonee Matsko:** Writing – review & editing, Project administration, Investigation, Data curation. **Amy Colaizzi:** Writing – review & editing, Project administration, Investigation. **Stephanie Wharton:** Writing – review & editing, Project administration, Formal analysis. **Rohit Bhargava:** Writing – review & editing, Supervision, Resources, Methodology, Formal analysis. **Matthew Hanna:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Sarah Harrington:** Writing – review & editing, Methodology. **Liron Pantanowitz:** Writing – review & editing, Visualization, Resources, Methodology, Formal analysis, Conceptualization. **Chengquan Zhao:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis, Conceptualization.

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