

Urine and Vaginal Self-Sampling for HR-HPV and CIN2+/CIN3+ Detection in Cervical Cancer Screening: A Narrative Review of Diagnostic Accuracy, Heterogeneity, and Implementation Considerations

Thimoléon Kizito Agbessy¹, Patrice Hodonou Avogbe^{1*}, Christelle Yelognisse Ahomadegbe², Arnaud Zinsou Vinouyon Henry¹, Ezékéel Judicaël Bocovo², Adeola Zouri Kifouli Adeoti³, Ambaliou Sanni⁴

¹Genomic Epidemiology Research Unit, Tropical Infectious Disease Research Center, Faculty of Sciences and Techniques, University of Abomey-Calavi, Abomey-Calavi, Benin

²Unit of Pathological Anatomy and Medical Oncology, Porto-Novo, Benin

³Laboratory of Microbiology and Food Technology, Faculty of Sciences and Techniques, University of Abomey-Calavi, Cotonou, Benin

⁴Laboratory of Biochemistry and Molecular Biology, University of Abomey-Calavi, Cotonou, Benin

Email: *Patrice.avogbe@gmail.com

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Abstract

Background: Cervical cancer remains a major global health burden, disproportionately affecting women in low- and middle-income countries where screening coverage is limited. While HPV-based screening is highly effective, clinician collected sampling poses logistical and sociocultural barriers. Self-sampling approaches, including vaginal and urine-based HPV testing, have emerged as potential strategies to expand access. However, uncertainties remain regarding their comparative diagnostic accuracy and optimal implementation conditions. This narrative review synthesizes evidence on the diagnostic accuracy of urine and vaginal self-sampling versus clinician collected samples for detecting cervical HPV infection and cervical intraepithelial neoplasia grade 2 or worse (CIN2+). **Methods:** A narrative review of diagnostic accuracy studies published up to March 2026 was conducted. PubMed/MEDLINE was systematically searched and supplemented by manual screening of reference lists. Studies were eligible if they evaluated HPV detection using urine and/or self-collected vaginal samples, included a paired clinician collected cervical sample, and reported at least one of the following reference standards: histo-

logically confirmed CIN2+ or CIN3+, histologically confirmed HSIL+, or cervical HR-HPV DNA detection. Data were synthesized separately by endpoint, and then compared across population settings (screening, referral, and high-risk groups), assay type, cut off strategies, and pre-analytical conditions such as first void versus random urine and preservation methods. **Results:** Across 51 studies, urine-based HR-HPV testing showed moderate-high sensitivity for CIN2+/CIN3+ (about 75% - 80%) but modest specificity (around 50% - 60%), with best performance when first void urine, proper preservation, and PCR-based assays were used. Vaginal self-sampling generally achieved higher sensitivity (often >90%) and better specificity (about 65% - 85%), approaching clinician collected samples when PCR assays and optimized cut offs were applied. For HSIL+, evidence was sparse: one large study reported almost perfect accuracy for urine testing, and no robust HSIL only data were available for vaginal sampling. For HR-HPV detection using cervical HPV as reference, urine reached sensitivities around 75% - 85% and specificities near 90%, while vaginal self-sampling exceeded 90% sensitivity with slightly lower specificity. **Conclusion:** Self-sampling with vaginal and urine specimens shows clinically meaningful accuracy for both HR-HPV and CIN2+/CIN3+ detection, supporting wider cervical cancer screening in women who avoid pelvic examinations. Vaginal self-sampling with validated PCR assays and optimized cut offs generally matches clinician collected samples for CIN2+/CIN3+ and is already WHO endorsed. Urine-based testing, when based on first void collection and robust pre-analytical protocols, achieves moderate-high sensitivity for CIN2+/CIN3+ and high accuracy for HR-HPV, making it particularly suitable for hard to reach or stigmatized groups. Standardized self-sampling procedures, validated assays, and endpoint specific interpretation are essential, and offering both vaginal and urine options is likely to maximize participation and accelerate progress toward cervical cancer elimination targets.

Keywords

Cervical Cancer Screening, CIN2+/CIN3+ Detection, Diagnostic Accuracy, High-Risk Human Papillomavirus (HR-HPV), Sensitivity, Specificity, Urine Self-Sampling, Vaginal Self-Sampling

1. Introduction

Cervical cancer remains one of the most preventable yet deadly malignancies among women globally. Each year, more than 600,000 new cases and 340,000 deaths are recorded, with nearly 90% of this burden concentrated in low- and middle-income countries (LMICs) [1] [2]. Persistent infection with high-risk human papillomavirus (HR-HPV) is recognized as the indispensable cause of cervical carcinogenesis, making effective prevention dependent on vaccination, early detection and treatment before invasive disease develops. However, despite this well-established etiology, translation of HPV-based screening into population-

level impact remains uneven globally, particularly where health systems lack the resources for repeated clinician-based testing.

In 2020, the World Health Organization launched its Global Strategy to Accelerate the Elimination of Cervical Cancer, setting the “90-70-90” targets for 2030: 90% HPV vaccination coverage among girls aged 9 - 14, 70% of women screened twice by age 45 using high-performance tests, and 90% of those with precancer or cancer receiving appropriate treatment [3]. Progress toward these targets remains especially difficult in LMICs, where health systems are often under-resourced, clinical infrastructure is limited, and access to pelvic examination is constrained [4]. Provider-collected cervical sampling is invasive, resource-intensive, and can evoke discomfort or stigma, discouraging participation in conservative cultural contexts [5]. Consequently, population-level screening coverage remains below 20% in large parts of sub-Saharan Africa and South Asia, and up to half of eligible women have never been tested [6]. This persistent coverage gap underscores the urgent need for alternative sampling strategies that are acceptable, scalable, and do not rely on pelvic examination.

To close this coverage gap, self-collected sampling has emerged as a transformative strategy. Vaginal self-sampling has been studied for over two decades; by 2010, PCR-based HPV assays on self-collected vaginal samples showed sensitivity and specificity for cervical intraepithelial neoplasia grade 2 or worse (CIN2+) comparable to clinician-collected cervical samples [7]. Subsequent meta-analyses confirmed that vaginal self-collection provides robust accuracy when analyzed with signal-amplification or PCR-based assays [8]. This evidence led the WHO and other professional societies to recommend vaginal self-sampling as an alternative in hard-to-reach populations [9]. Community-based programs have demonstrated that self-sampling can rapidly scale up screening—for instance, screening hundreds of thousands of women within short timeframes. However, while vaginal self-sampling has become established, it still requires genital sampling, which some women may find unacceptable (cultural or religious barriers) or difficult to perform correctly—limitations that urine sampling could potentially overcome.

Urine is an even more universally accepted sample type because it is completely non-invasive, requires no genital access, and can be collected at home without specialized training [10]. Over two decades of methodological refinement have shown that pre-analytical factors—such as urine fraction (first-void vs. random), preservation methods, and extraction efficiency—have historically caused wide variability in diagnostic performance [11] [12]. Optimized first-void collection devices and better DNA extraction and concentration methods have increased HPV yield and improved concordance with cervical samples. As a result, urine testing is no longer viewed only as a theoretical possibility, but as a practical screening approach that is again attracting clinical and public health interest. Nevertheless, reported diagnostic accuracy for urine still varies widely across studies (sensitivity 74% - 83%, specificity 51% - 91% for CIN2+), and no consensus exists on whether urine-based HPV testing is ready for routine screening [13] [14]. Im-

portantly, many of these estimates come from referral populations with higher disease prevalence, limiting generalizability to screening settings.

Moreover, direct comparisons between urine and vaginal self-sampling in the same population are sparse, and sources of heterogeneity—including assay platform, cut-off thresholds, collection devices, pre-analytical handling, and epidemiologic context (screening vs. referral vs. high-risk groups)—remain poorly understood [15] [16]. In addition, studies often differ in their outcomes, ranging from cervical HPV positivity to histologically confirmed CIN2+ or cervical cancer, which further complicates comparison across studies. Given these uncertainties, a structured synthesis of the evidence is needed to guide clinical and public health decisions, especially in resource-limited settings. Such a synthesis is particularly timely because implementation decisions require not only proof of diagnostic accuracy, but also clarity about when urine may be a practical substitute and when vaginal self-sampling remains preferable.

This narrative review fills that gap by systematically synthesizing the available evidence on urine- and vaginal self-sampling for HPV detection and CIN2+ outcomes. The objectives are to: 1) summarize the overall diagnostic accuracy of urine-based and vaginal self-collected HPV testing for detecting cervical HPV infection and CIN2+/CIN3+; 2) compare performance between urine and vaginal self-samples; 3) identify key sources of heterogeneity, including assay technology, pre-analytical factors, and population characteristics (screening vs. referral vs. high-risk groups); and 4) discuss clinical implications and research gaps for implementation in LMICs. Accordingly, this review focuses on whether self-sampling methods can expand screening coverage while preserving clinically meaningful accuracy, and on the methodological conditions required for reliable implementation.

2. Methods

2.1. Information Sources and Search Strategy

PubMed/MEDLINE was searched as the primary database. The search combined terms related to specimen type, HPV testing, and diagnostic accuracy, including “urine”, “urine-based”, “vaginal self-sampling”, “HPV testing”, “human papillomavirus”, “cervical cancer screening”, “diagnostic accuracy”, “sensitivity”, “specificity”, and “concordance”. MeSH terms and free-text keywords with Boolean operators were used to maximize retrieval. In addition, the reference lists of relevant articles and identified systematic reviews were manually screened to identify additional studies. The search was limited to human studies published in English, with no geographical restrictions.

2.2. Eligibility Criteria

Studies were included if they reported diagnostic accuracy of HPV testing in urine samples, self-collected vaginal samples, or both, compared with clinician-collected cervical samples. The reference standard could be HPV DNA detection in cervical

specimens or histologically confirmed cervical intraepithelial neoplasia grade 2 or worse (CIN2+). Eligible studies involved human participants from screening, referral, or high-risk populations and were published as original research articles in peer-reviewed English-language journals up to March 2026. Systematic reviews and meta-analyses were retained for background context. Studies were excluded if they were editorials or lacked sufficient information to extract diagnostic performance metrics. Narrative reviews, scoping reviews, and any review that did not apply a systematic search strategy or provide quantitative meta-analytic estimates were excluded.

2.3. Data Extraction

Data were extracted from each included study. Extracted variables included first author, publication year, population characteristics, sample size, risk category, sample types tested (urine, self-collected vaginal, clinician-collected cervical), HPV assay platform, reference standard details, and diagnostic accuracy metrics such as sensitivity, specificity, percent agreement, Cohen's kappa, and relative sensitivity or specificity when reported. For meta-analyses used for background, pooled estimates and 95% confidence intervals were retrieved.

2.4. Definitions of Population Categories and Reference Standards

Population groups were assigned based on the recruitment setting and clinical context described in each primary study. Screening populations comprised asymptomatic individuals participating in organized or opportunistic cervical cancer screening programs, with no prior abnormal cytology or known HPV infection. Referral populations included individuals referred for colposcopy due to an abnormal screening test (e.g., positive HPV test, High-grade squamous intraepithelial lesion [HSIL]) or directly from colposcopy clinics, thereby representing a higher pretest probability of CIN2+/CIN3+. High-risk populations were defined as individuals with known risk factors for HPV persistence or cervical disease, such as HIV infection or previous treatment for cervical lesions, but not necessarily referred for colposcopy at enrolment. For diagnostic accuracy estimates, the reference standard was specified as either 1) HPV DNA detection from clinician-collected cervical samples (using the same PCR-based assay as applied to urine or self-collected vaginal samples), or 2) histologically confirmed endpoints (CIN2+, CIN3+, or cancer) based on colposcopy-directed biopsy or excisional procedure. HPV detection endpoints were used only when histology was not available or when the outcome of interest was agreement for HPV positivity rather than lesion identification. This classification was applied consistently during data extraction to allow narrative comparison across subgroups.

2.5. Synthesis Methods

No meta-analysis was performed. Data from primary studies were synthesized narratively and organized thematically into overall diagnostic accuracy, direct

comparisons between urine and vaginal self-sampling, population differences, assay technology and cut-off effects, pre-analytical factors, and agreement statistics. Comparable outcomes across studies were summarized using ranges and patterns rather than pooled estimates. Sources of heterogeneity, including population characteristics, collection methods, and assay differences were explored qualitatively.

3. Results

From an initial pool of 110 records, 51 studies met the eligibility criteria, including 41 primary diagnostic-accuracy studies and 10 meta-analyses providing pooled estimates (**Table 1**). Of the 41 primary studies, 23 compared urine HPV testing with clinician-collected cervical samples (**Table 2**) and 18 evaluated urine and vaginal self-sampling against clinician-collected samples (**Table 3**). Diagnostic performance was examined separately for CIN2+/CIN3+, HSIL+, and HR-HPV detection, allowing endpoint-specific estimates of sensitivity and specificity that are directly applicable to different clinical decisions (screening, triage, or surveillance).

Table 1. Meta-analytic summary of self-sampling performance for HR-HPV/CIN2+ detection compared with clinician-collected cervical samples across mixed populations.

Authors	Sample types	Assay (method)	Sensitivity (outcome) % (95% CI)	Specificity (outcome) % (95% CI)	Clinical Outcomes
Jeevika <i>et al.</i> [17]	Urine vs cervical	Various HPV assays (PCR-based)	(CIN2+) 74% (67 - 80)	(CIN2+) 52% (43 - 61)	CIN2+ detection
Ye <i>et al.</i> [18]	Urine vs cervical; also vaginal	Various HPV assays	(Cervical HPV detection) 76% (72 - 80); (CIN2+) 79% (72 - 84)	(Cervical HPV detection) 90% (87 - 92); (CIN2+) 58% (50 - 65)	CIN2+ detection
Hsiao <i>et al.</i> [19]	Urine self-collected	HPV NAAT (DNA-based)	(HSIL+/CIN2+) 83.0% (77.5 - 87.3)	(HSIL+/CIN2+) 51.3% (39.2 - 63.3)	HSIL and CIN2+ detection
Li <i>et al.</i> [21]	Vaginal and urine self-sampling vs cervical	HPV PCR	(HR-HPV) vaginal 92% (90 - 94), urine 83% (77 - 88); (>CIN2) vaginal 98% (96 - 99), urine 95% (91 - 97)	(HR-HPV) vaginal 80% (58 - 92), urine 81% (65 - 91); (>CIN2) vaginal 63% (48 - 77), urine 62% (31 - 86)	CIN2+ detection
Park <i>et al.</i> [48]	Urine vs cervical	Real-time PCR assays	(HPV detection) 82% (78 - 86)	(HPV detection) 91% (87 - 94)	HR-HPV detection
Arbyn <i>et al.</i> [7]	Self-collected vaginal vs cervical	Various (signal-based and PCR)	(CIN2+) 76% (69 - 82); (CIN3+) 84% (72 - 92)	(CIN2+) 86% (83 - 89); (CIN3+) 87% (84 - 90)	HR-HPV detection
Cho <i>et al.</i> [14]	Urine vs cervical	Various PCR-based	Relative sensitivity for CIN2+: 0.84 (0.78 - 0.91)*	Relative specificity: 1.06 (1.03 - 1.10)*	CIN2+ detection
Pathak <i>et al.</i> [13]	Urine vs cervical	Various commercial PCR	(Any HPV) 87% (78 - 92); (HR-HPV) 77% (68 - 84); (HPV16/18) 73% (56 - 86)	(Any HPV) 94% (82 - 98); (HR-HPV) 88% (58 - 97); (HPV16/18) 98% (91 - 100)	HR-HPV detection

Continued

Arbyn <i>et al.</i> [8] [†]	Self-collected vaginal vs cervical	PCR-based HR-HPV assays	Relative sensitivity for CIN2+/CIN3+: 0.99 (0.97 - 1.02)*	Relative specificity for CIN2+: 0.98 (0.96 - 0.99)*	CIN2+/CIN3+ detection
Arbyn <i>et al.</i> [20] [‡]	Self-collected vaginal vs cervical	APTIMA mRNA vs validated DNA assays	Relative sensitivity for CIN2+: 0.98 (0.95 - 1.01); for CIN3+: 0.98 (0.95 - 1.01)*	Relative specificity for CIN2+: 1.03 (1.02 - 1.04)*	CIN2+/CIN3+ detection

Footnotes: *Relative sensitivity/specificity ratios compare urine performance to clinician-collected cervical samples (ratio = urine accuracy/cervical accuracy). A value of 1.00 indicates identical accuracy. Note: Meta-analyses generally included mixed populations (screening, referral, high-risk). [†], [‡] The Arbyn *et al.* (2018) and (2022) papers primarily address vaginal self-sampling or mRNA testing on clinician-collected samples, not urine. Abbreviations: NR = not reported; CIN2+ = cervical intraepithelial neoplasia grade 2 or worse; HSIL+ = high-grade squamous intraepithelial lesion or worse; HR-HPV = high-risk human papillomavirus; PCR = polymerase chain reaction; NAAT = nucleic acid amplification test.

Table 2. Diagnostic accuracy of urine HPV testing compared with clinician-collected cervical samples.

Authors	Population	Sample Types	Assay (method)	Agreement	Sensitivity (outcome) % (95% CI)	Specificity (outcome) % (95% CI)	Sample Size	Clinical Outcomes
Davies <i>et al.</i> [22]	Screening	Urine vs cervical	Roche Cobas® 8800 (PCR, DNA)	91.8% (κ = 0.68)	(CIN2+) 96.0% (79 - 100)	(CIN2+) 85% (83 - 87)	1517	CIN2+ detection
Intan <i>et al.</i> [50]	Colposcopy referral	Urine vs cervical	HR-HPV ReadyMix qPCR vs Roche Cobas 6800	89.8% (κ = 0.89)	(HR-HPV detection) 80.9%	(HR-HPV detection) 100%	876	HR-HPV detection
Van Keer <i>et al.</i> [24]	Colposcopy referral	Urine vs cervical	Cobas 4800/6800 (PCR, DNA)	κ = 0.68 - 0.87	Relative sensitivity ratio for CIN2+: 0.98 (0.93 - 1.02)/0.96 (0.91 - 1.02) [†]	Relative specificity ratio for <CIN2: 1.00 (0.91 - 1.10)/1.01 (0.93 - 1.09) [†]	499	CIN2+ detection
Van Keer <i>et al.</i> [25]	Colposcopy referral	Urine vs cervical	Abbott Alinity m HR-HPV (PCR, DNA)	κ = 0.64 - 0.85	Relative sensitivity ratio for CIN2+: 0.91 - 0.96 [†]	Relative specificity ratio: 1.04 - 1.00 [†]	297	CIN2+ detection
Zhao <i>et al.</i> [28]	Colposcopy referral	Urine vs cervical	CerviClear® (ABI7500 RT-PCR)	κ = 0.51	(CIN2+) urine: 87.7%; cervical: 85.5%	(CIN2+) urine: 33.5%; cervical: 26.9%	732	CIN2+ and CIN3+ detection
Kaoma <i>et al.</i> [49]	High-risk screening (HIV+)	Urine vs cervical	GeneXpert (PCR, DNA)	89.8% (κ = 0.77)	(HR-HPV) 84.8% (68.1 - 94.9)	(HR-HPV) 92.3% (83.0 - 97.5)	100	HR-HPV detection
Van Keer <i>et al.</i> [26]	Colposcopy referral	Urine vs cervical	BD Onclarity HPV Assay (PCR, DNA)	κ = 0.56 - 0.85	Relative sensitivity ratio for CIN2+: 1.00 (0.93 - 1.07) [†]	Relative specificity ratio for <CIN2: 0.92 (0.84 - 0.996) [†]	492	CIN2+ detection

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Punyashthira <i>et al.</i> [32]	Referral (abnormal Pap)	Urine vs cervical	Anyplex™ II HPV HR (PCR, DNA)	$\kappa = 0.86$ (HPV16/18)	(CIN2+) urine: 86.2%; cervical: 94.8%	NR	96	CIN2+ detection
Van Keer <i>et al.</i> [27]	Colposcopy referral	Urine vs cervical	Abbott RealTime High-risk HPV (PCR, DNA)	NR	Relative sensitivity ratio for CIN2+: 0.95 (0.88 - 1.01) [†]	Relative specificity ratio for <CIN2: 1.03 (0.95 - 1.13) [†]	~500	CIN2+ detection
Lee <i>et al.</i> [51]	General (screening-based diagnostic validation)	Urine vs cervical	Cobas HPV test (PCR, DNA)	90.4% ($\kappa = 0.90$)	(HPV16) 81.3%; (HPV18) 100%; (other HR-HPV) 96.4% [‡]	(HPV16) 98.0%; (HPV18) 95.3%; (other) 100% [‡]	67	HPV detection
Xu <i>et al.</i> [23]	Screening	Urine vs cervical	careHPV/cobas4800 HPV test	86.6% ($\kappa = 0.48$)/83% ($\kappa = 0.46$)	(CIN2+) careHPV: 85.7%; cobas: 69.2%	(CIN2+) careHPV: 86.8%; cobas: 82.3%	2038	CIN2+ detection
Maged <i>et al.</i> [47]	Referral (colposcopy)	Urine vs cervical (pathology)	PCR for high-risk HPV	NR	(HSIL) 97.8% (92.1 - 99.7)	(HSIL) 100% (99.7 - 100)	1375	HSIL detection
Lorenzi <i>et al.</i> [29]	Referral (CIN2+ enriched)	Urine vs cervical	HPV-HR test (urine) vs Cobas (cervical)	79.8% ($\kappa = 0.363$)	(CIN2+) urine: 83.4% (78.4 - 87.6)	(CIN2+) urine: 50.8% (33.7 - 59.0)	336	CIN2+/CIN3+ detection
Vergara <i>et al.</i> [52]	Screening	Urine vs cervical	Real-time PCR + PCR-RLB	86.2% ($\kappa = 0.72$)	(Any HR-HPV) 82.7% (78.0 - 86.8)	(Any HR-HPV) 94.6% (90.9 - 97.1)	543	HPV detection
Tshomo <i>et al.</i> [53]	Follow-up (HPV+ normal cytology)	Urine vs cervical	Multiplex PCR (E7-MPG)	NR	(21 HPV types) 80% (67 - 90)	(21 HPV types) 61% (43 - 76)	89	HPV detection
Cuzick <i>et al.</i> [15]	Referral (colposcopy)	Urine vs cervical	Trovagene HPV test	82.6% ($\kappa = 0.46$, 0.37 - 0.56)	(CIN2+) 88.3% (81.9 - 93.0)	(CIN2+) 24.7% (20.3 - 29.5)	501	CIN2+/CIN3+ detection
Lim <i>et al.</i> [54]	Screening (assay comparison)	Urine vs cervical	Roche cobas 4800/Abbott RealTime	86.0% ($\kappa = 0.717$)	(HPV16/18) Roche 79.2% (57.9 - 92.9); Abbott 81.8% (59.7 - 94.8)	(HPV16/18) Roche 100% (95.3 - 100); Abbott 100% (95.4 - 100)	100	HPV detection
Combata <i>et al.</i> [55]	Screening-follow-up	Urine vs cervical	Multiplex type-specific genotyping (Luminex)	$\kappa = 0.54 - 0.81$	(Any HPV) 90.6% (87.0 - 94.0); (HPV6/11/16/18) 62% - 100%	(Any HPV) 74.1% (68.0 - 80.0); (HPV6/11/16/18) 96% - 99%	535	HPV detection

Continued

Sahasrabuddhe <i>et al.</i> [30]	Colposcopy referral	Urine vs cervical	Linear Array HPV Genotyping Test	$\kappa = 0.57$	(CIN2/3) 80.8% (60.6 - 93.4)	(CIN2/3) 42.2% (27.7 - 57.8)	72	CIN2/3 detection
Tanzi <i>et al.</i> [56]	Screening/ high-risk (HIV+)	Urine vs cervical	PCR + RFLP	$\kappa = 0.96$ (0.90 - 1.0)	(HPV detection) 98.6% (93.1 - 99.9)	(HPV detection) 97.4% (87.7 - 99.9)	107	HPV detection
Daponte <i>et al.</i> [31]	Referral (abnormal cytology)	Urine vs cervical	Commercial PCR (HPV16/18)	$\kappa = 0.51$ (high grade); 0.19 (low grade)	(Cancer) 88.8% (51.8 - 99.7); (high-grade) 76.5% (50.1 - 93.2); (low-grade) 45.5% (16.7 - 76.6)	(HPV16/18) 100% (94.0 - 100)	100	HPV detection
Xu <i>et al.</i> [23]	Screening (population-based)	Urine vs cervical	careHPV/cobas 4800	86.6% ($\kappa = 0.48$)/83% ($\kappa = 0.46$)	careHPV: 85.7% (48.7 - 97.4); cobas: 69.2% (42.4 - 87.3)	careHPV: 86.8% (84.5 - 88.8); cobas: 82.3% (79.8 - 84.5)	2038	CIN2+ detection
Davies <i>et al.</i> [33]	Colposcopy referral	Urine vs cervical	Roche Cobas® 8800 (PCR, DNA)	NR	(CIN2+) 90.3% (83.7 - 94.9)	NR	235	CIN2+ detection

Footnotes: [†]Relative sensitivity/specificity ratios compare urine to clinician-collected cervical samples (ratio = urine performance/cervical performance). A value of 1.00 indicates identical accuracy. [‡]Lee *et al.* (2020) reported genotype-specific results for HPV16, HPV18, and other HR-HPV types. Abbreviations: NR = not reported; κ = Cohen's kappa; CIN2+ = cervical intraepithelial neoplasia grade 2 or worse; HSIL = high-grade squamous intraepithelial lesion; HR-HPV.

Table 3. Diagnostic accuracy of urine and vaginal self-sampling for HPV detection compared to clinician-collected cervical samples.

Authors	Population	Sample Types	Assay (method)	Agreement	Sensitivity (outcome) % (95% CI)	Specificity (outcome) % (95% CI)	Sample Size	Clinical Outcomes
Cuschieri <i>et al.</i> [16]	Colposcopy referral (multicentre)	Urine, vaginal self-sample vs cervical	Papilloplex HR-HPV assay (PCR, DNA)	NR	Relative sensitivity ratio for CIN2+: urine 0.95 (0.88 - 1.03); vaginal 1.05 (1.01 - 1.09) [†]	Relative specificity ratio for <CIN2: urine 0.95 (0.88 - 1.03); vaginal 0.81 (0.74 - 0.89) [†]	494	CIN2+ detection
van den Borst <i>et al.</i> [34]	Colposcopy referral	Urine, vaginal self-sample vs cervical	EUROArray HPV test (PCR, DNA)	NR	Relative sensitivity ratio for CIN2+: urine 0.96 (0.90 - 1.05); vaginal 0.96 (0.91 - 1.02) [†]	Relative specificity ratio for <CIN2: urine 0.94 (0.85 - 1.04); vaginal 0.98 (0.91 - 1.07) [†]	494	CIN2+ detection

Continued

Xue <i>et al.</i> [36]	Screening	Urine, vaginal self-sample vs cervical	HR-HPV PCR	For CIN2+: 98.83% (urine); 98.82% (vaginal)	(CIN2+) urine 70.0% (35.4 - 91.9); vaginal 90.0% (54.1 - 99.5)	(CIN2+) urine 98.23% (97.56 - 98.72); vaginal 98.50% (97.87 - 98.95)	2228	CIN2+ detection
Latsuzbaia <i>et al.</i> [35]	Screening	Urine, vaginal self-sample vs cervical	Liferiver HarmoniaHPV (PCR, DNA)	NR	Relative sensitivity ratio for CIN2+: urine 0.95 (0.89 - 1.02); vaginal 0.95 (0.88 - 1.02) [†]	Relative specificity ratio for <CIN2: urine 0.95 (0.86 - 1.04); vaginal 0.93 (0.86 - 1.01) [†]	523 (499 triplets)	CIN2+ detection
Giubbi <i>et al.</i> [57]	Colposcopy referral	Urine, vaginal self-sample vs cervical	Anyplex™II HR-HPV (PCR, DNA)	$\kappa = 0.77$ (urine); $\kappa = 0.87$ (vaginal)	(HR-HPV detection) urine 93.4%; vaginal 99.1%	(HR-HPV detection) urine 83.5%; vaginal 85.0%	342	HR-HPV and STI detection
Yan <i>et al.</i> [37]	Referral (colposcopy)	Urine, vaginal self-sample vs cervical	Specific HR-HPV PCR	78.1% (urine); 85.7% (vaginal)	(CIN2+) urine 86.7%; vaginal 90.6%	(CIN2+) urine 36.5%; vaginal 30.5%	1588	CIN2+ detection
Giubbi <i>et al.</i> [42]	Colposcopy referral	Urine, vaginal self-sample vs cervical	OncoPredict HPV SCR (PCR, DNA)	$\kappa = 0.53 - 1.00$	Relative sensitivity ratio for CIN2+: urine 0.95 (0.88 - 1.02); vaginal 0.96 (0.90 - 1.02) [†]	Relative specificity ratio for <CIN2: urine 1.03 (0.96 - 1.12); vaginal 0.90 (0.84 - 0.96) [†]	500	CIN2+ detection
Latsuzbaia <i>et al.</i> [43]	Colposcopy referral	Urine, vaginal self-sample vs cervical	OncoPredict HPV QT (PCR, DNA)	NR	Relative sensitivity ratio for CIN2+: urine 0.99 (0.94 - 1.05); vaginal 1.00 (0.96 - 1.04) [†]	Relative specificity ratio for <CIN2: urine 0.91 (0.84 - 0.98); vaginal 0.90 (0.84 - 0.98) [†]	490	CIN2+ detection
Latsuzbaia <i>et al.</i> [44]	Colposcopy referral	Urine, vaginal self-sample vs cervical	Alinity m HR-HPV (PCR, DNA)	$\kappa = 0.72$ (urine); $\kappa = 0.79$ (vaginal)	Relative sensitivity ratio for CIN2+: urine 0.94 (0.85 - 1.03); vaginal 0.92 (0.85 - 1.00) [†]	Relative specificity ratio for <CIN2: urine 1.02 (0.95 - 1.10); vaginal 1.08 (1.01 - 1.15) [†]	492	CIN2+ detection
Ornskov <i>et al.</i> [41]	Colposcopy referral	Urine, vaginal self-sample vs cervical	Cobas HPV assay (PCR, DNA)	NR	Relative sensitivity for CIN2+: vaginal 1.00 (0.96 - 1.04); urine 0.96 (0.91 - 1.03) [†]	Relative specificity for <CIN2: vaginal 1.03 (0.95 - 1.12); urine 0.98 (0.89 - 1.09) [†]	305	CIN2+/CIN3+ detection

Continued

Kuriakose <i>et al.</i> [59]	Screening	Urine vs vaginal self-sample (no cervical)	Multiplex real-time PCR + L1 PCR	64.0% ($\kappa = 0.29$)	(HR-HPV detection) urine vs vaginal: 57.9% (47.5 - 67.7) [‡]	(HR-HPV detection) urine vs vaginal: 84.6% (66.4 - 93.8) [‡]	114	HR-HPV detection
Stanczuk <i>et al.</i> [38]	Screening	Urine, vaginal self-sample vs cervical	Cobas 4800 (PCR, DNA)	$\kappa = 0.693$	(CIN2+) vaginal 94.6% (90.7 - 98.5); urine 63.1% (54.6 - 71.7)	(CIN2+) vaginal 85.4% (84.4 - 86.3); urine 89.8% (89.0 - 90.7)	5318	CIN2+ detection
Senkomago <i>et al.</i> [40]	Colposcopy referral	Urine, vaginal self-sample vs cervical	Trovagene test	NR	(CIN2+) urine 89.9% (62.7 - 99.6); vaginal 79.1% (48.1 - 96.6)	(CIN2+) urine 34.8% (18.4 - 54.1); vaginal 46.2% (27.9 - 65.2)	37	CIN2+ detection
Mizuno <i>et al.</i> [58]	Abnormal cytology cohort	Urine, vaginal self-sample vs cervical	BD Onclarity [®] HPV (PCR, DNA)	Urine: 63.9% ($\kappa = 0.34$); vaginal: 77.8% ($\kappa = 0.68$)	(HPV detection) urine 46.4% (36.0 - 57.1); vaginal 75.7% (65.7 - 85.6)	(HPV detection) urine 77.1% (60.2 - 88.5); vaginal 69.0% (52.2 - 85.7)	121	HPV detection
Martinelli <i>et al.</i> [39]	Colposcopy referral	Urine, vaginal self-sample vs cervical	Anyplex [™] II HPV28 (PCR, DNA)	$\kappa = 0.792$ (urine); 0.898 (vaginal)	(CIN2+) urine 90.9% (82.4 - 99.4); vaginal 95.5% (89.3 - 100)	(CIN2+) urine 39.8% (30.0 - 46.6); vaginal 36.3% (29.7 - 43.0)	245	CIN2+ detection
Mathews <i>et al.</i> [46]	Screening	Vaginal self-sample vs cervical	cobas HPV DNA; APTIMA HPV mRNA	Range 75.8% - 96.5%	Relative sensitivity for CIN2+: 0.77 - 0.94 (depending on workflow) [†]	Relative specificity: 0.87 - 0.99 [†]	1000	CIN2+ detection
Xu <i>et al.</i> [45]	Screening	Vaginal self-sample vs cervical	careHPV; GenPlex	79.0% ($\kappa = 0.563$); 80.5% ($\kappa = 0.605$)	(CIN2) careHPV: 77.4%; GenPlex: 100%	(CIN2) careHPV: 71.0%; GenPlex: 58.7%	732	CIN2 detection
Tranberg <i>et al.</i> [60]	Referral (ASC US positive)	Urine, vaginal self-sample vs cervical	COBAS [®] 4800 (PCR, DNA)/GENOMICA CLART [®] (PCR, DNA)	$\kappa = 0.66$ (0.52 - 0.79)/88.7% (urine vs cervical) $\kappa = 0.66$ (0.51 - 0.81) [§]	(HR-HPV detection) urine vs vaginal 59.1% (43.2 - 73.7)/urine vs cervical 63.9% (46.2 - 79.2) [§]	(HR-HPV detection) urine vs vaginal 99.1% (94.9 - 99.7)/urine vs cervical 96.5% (91.3 - 99.0) [§]	150	HR-HPV detection

Footnotes: [†]Relative sensitivity/specificity ratios compare self-sample performance to clinician-collected cervical samples (ratio = self-sample accuracy/cervical accuracy). A value of 1.00 indicates identical accuracy. [‡]Kuriakose *et al.* (2020) did not use a cervical gold standard; values represent urine accuracy relative to vaginal self-sampling. [§]In the Tranberg *et al.* study, urine was compared to both vaginal self-samples and cervical samples; therefore, two sets of agreement, sensitivity, and specificity are provided (urine vs vaginal/urine vs cervical). Unlike most included studies, the vaginal comparison does not use a cervical reference. Abbreviations: NR = not reported; κ = Cohen's kappa; CIN2+ = cervical intraepithelial neoplasia grade 2 or worse; HR-HPV = high-risk human papillomavirus; PCR = polymerase chain reaction; DNA = deoxyribonucleic acid; mRNA = messenger ribonucleic acid.

3.1. CIN2+/CIN3+ Detection

3.1.1. Meta-Analytic Evidence: Pooled Summary Estimates for CIN2+/CIN3+ Detection (Table 1)

For urine-based HR-HPV testing targeting histologically confirmed CIN2+, Jeevika *et al.* [17] reported a pooled sensitivity of 74% (95% CI: 67 - 80) and specificity of 52% (43 - 61) from five studies. Ye *et al.* [18] found similar estimates across 31 studies: sensitivity 79% (72 - 84) and specificity 58% (50 - 65) for CIN2+. Using a broader endpoint that combined HSIL+ and CIN2+, Hsiao *et al.* [19] reported a pooled sensitivity of 83.0% (77.5 - 87.3) and specificity of 51.3% (39.2 - 63.3) for urine nucleic acid amplification tests. For vaginal self-sampling, Arbyn *et al.* [7] showed a pooled sensitivity of 76% (69 - 82) for CIN2+ and 84% (72 - 92) for CIN3+, with specificities of 86% (83 - 89) and 87% (84 - 90), respectively. In an updated analysis, Arbyn *et al.* [8] demonstrated that PCR-based HR-HPV assays on self-collected vaginal samples had a relative sensitivity for CIN2+/CIN3+ of 0.99 (0.97 - 1.02) and a relative specificity of 0.98 (0.96 - 0.99) compared with clinician collected samples. For mRNA testing on clinician collected samples, Arbyn *et al.* [20] reported relative sensitivities for CIN2+ and CIN3+ of 0.98 (0.95 - 1.01) each; however, on self-collected vaginal samples the same mRNA assay (AP-TIMA) showed a lower relative sensitivity of 0.84 (0.74 - 0.96) for CIN2+. Cho *et al.* [14] calculated a pooled relative sensitivity for urine HPV testing of 0.84 (0.78 - 0.91) for CIN2+. In a head-to-head meta-analysis, Li *et al.* [21] found that for >CIN2 lesions, vaginal self-sampling achieved a sensitivity of 98% (96 - 99) and specificity of 63% (48 - 77), while urine testing gave 95% (91 - 97) sensitivity and 62% (31 - 86) specificity.

3.1.2. Primary Studies: Urine versus Cervical Samples for CIN2+/CIN3+ Detection (Table 2)

In a screening population of 1517 women, Davies *et al.* [22] reported that first void urine detected 24 of 25 CIN2+ cases (sensitivity 96.0%, 95% CI 79 - 100) with a specificity of 85% (83 - 87). Xu *et al.* [23] compared two assays in 2,038 screening participants: careHPV gave a CIN2+ sensitivity of 85.7% (48.7 - 97.4) and specificity 86.8% (84.5 - 88.8), whereas cobas4800 yielded 69.2% (42.4 - 87.3) sensitivity and 82.3% (79.8 - 84.5) specificity. In referral populations, Van Keer and colleagues reported relative sensitivity ratios (urine/cervical) for CIN2+ of 0.96 - 0.98 with Cobas assays [24], 0.91 - 0.96 with Abbott Alinity m [25], 1.00 (0.93 - 1.07) with BD Onclarity [26], and 0.95 (0.88 - 1.01) with Abbott RealTime [27]. Zhao *et al.* [28] found that urine had a CIN2+ sensitivity of 87.7% (vs. cervical 85.5%) but low specificity (33.5% vs. 26.9%) in a referral cohort of 732 women. Cuzick *et al.* [15] reported a high CIN2+ sensitivity of 88.3% (81.9 - 93.0) for urine but very low specificity (24.7%, 20.3 - 29.5) in a colposcopy referral population. Lorenzi *et al.* [29] observed a CIN2+ sensitivity of 83.4% (78.4 - 87.6) and specificity of 50.8% (33.7 - 59.0) in an enriched referral cohort. For CIN2/3 detection, Sahasrabuddhe *et al.* [30] reported urine sensitivity of 80.8% (60.6 - 93.4) and specificity of 42.2% (27.7 - 57.8). Daponte *et al.* [31] found that for cervical cancer, urine sensitivity

was 88.8% (51.8 - 99.7), and for high grade lesions it was 76.5% (50.1 - 93.2). Punyashthira *et al.* [32] reported a urine sensitivity for CIN2+ of 86.2% (cervical 94.8%) in women referred with abnormal Pap smears. Davies *et al.* [33] found a CIN2+ sensitivity of 90.3% (83.7 - 94.9) in a colposcopy referral cohort.

3.1.3. Primary Studies: Urine and Vaginal Self-Sampling versus Cervical Samples for CIN2+/CIN3+ Detection (Table 3)

In the VALHUDES framework, Cuschieri *et al.* [16] reported relative sensitivity ratios for CIN2+ of 0.95 (0.88 - 1.03) for urine and 1.05 (1.01 - 1.09) for vaginal self-samples, with corresponding relative specificities of 0.95 and 0.81. van den Borst *et al.* [34] found identical relative sensitivity of 0.96 for both sample types, with specificities of 0.94 (urine) and 0.98 (vaginal). Latsuzbaia *et al.* [35] reported relative sensitivity of 0.95 for both urine and vaginal self-samples and relative specificities of 0.95 and 0.93, respectively. In a screening population of 2228 women, Xue *et al.* [36] found that for CIN2+ detection, urine sensitivity was 70.0% (35.4 - 91.9) and vaginal sensitivity 90.0% (54.1 - 99.5), with very high specificities (>98% for both). Yan *et al.* [37] reported CIN2+ sensitivities of 86.7% (urine) and 90.6% (vaginal) with low specificities (36.5% and 30.5%, respectively) in a referral cohort of 1,588 women. Stanczuk *et al.* [38] demonstrated that vaginal self-sampling (Cobas 4800) had a CIN2+ sensitivity of 94.6% (90.7 - 98.5) compared with 63.1% (54.6 - 71.7) for urine, while specificity was 85.4% (84.4 - 86.3) for vaginal and 89.8% (89.0 - 90.7) for urine. Martinelli *et al.* [39] found CIN2+ sensitivities of 90.9% (urine) and 95.5% (vaginal), with low specificities (~40% and 36%). Senkomago *et al.* [40] reported CIN2+ sensitivities of 89.9% (urine) and 79.1% (vaginal) but very low specificities (34.8% and 46.2%) in a small referral cohort (n = 37). Ornskov *et al.* [41] showed relative sensitivities for CIN2+/CIN3+ of 1.00 (0.96 - 1.04) for vaginal and 0.96 (0.91 - 1.03) for urine. Multiple other VALHUDES related studies [42] [43] [44] consistently reported relative sensitivity ratios for CIN2+ between 0.92 and 1.00 for both sample types, with modestly lower specificity for vaginal self-samples in some analyses. Xu *et al.* [45] evaluated vaginal self-sampling alone for CIN2+ detection, reporting sensitivities of 77.4% (care-HPV) and 100% (GenPlex), with specificities of 71.0% and 58.7%, respectively. Mathews *et al.* [46] found that for CIN2+, vaginal self-sampling using cobas HPV DNA or APTIMA mRNA achieved relative sensitivities of 0.77 - 0.94 (depending on workflow) and relative specificities of 0.87 - 0.99.

3.2. HSIL Detection

Few studies used histologically confirmed high grade squamous intraepithelial lesion or worse (HSIL+) as the exclusive reference. In **Table 1**, the meta-analysis by Hsiao *et al.* [19] combined HSIL+ and CIN2+ outcomes, reporting a pooled sensitivity of 83.0% and specificity of 51.3% for urine NAATs; however, the endpoint was not reported separately for HSIL+ alone. In primary studies (**Table 2**), Maged *et al.* [47] evaluated urine HPV testing in 1375 women referred for colposcopy, using HSIL on histology as the reference. Urine testing achieved a sensitivity of

97.8% (92.1 - 99.7) and a specificity of 100% (99.7 - 100) for HSIL detection. No other primary study in this review reported HSIL+ as a distinct endpoint without mixing with CIN2+.

3.3. HR-HPV Detection

In this category, the reference standard is the detection of HR-HPV DNA in clinician collected cervical samples, without histological confirmation. These estimates reflect assay agreement rather than clinical disease detection.

3.3.1. Meta-Analytic Evidence: Pooled Summary Estimates for High-Risk Human Papillomavirus (HR-HPV) Genotypes (Table 1)

Park *et al.* [48] reported a pooled sensitivity of 82% (78 - 86) and specificity of 91% (87 - 94) for urine real time PCR assays targeting HR-HPV detection. Ye *et al.* [18] also provided a pooled estimate for cervical HPV detection of 76% sensitivity (72 - 80) and 90% specificity (87 - 92). Pathak *et al.* [13] found that urine testing had a sensitivity of 77% (68 - 84) for HR-HPV and 73% (56 - 86) for HPV16/18, with specificities of 88% (58 - 97) and 98% (91 - 100), respectively. For any HPV detection, Pathak *et al.* reported 87% sensitivity and 94% specificity. For vaginal self-sampling, Li *et al.* [21] reported HR-HPV detection sensitivities of 92% (90 - 94) for vaginal and 83% (77 - 88) for urine, with specificities of 80% (58 - 92) and 81% (65 - 91), respectively.

3.3.2. Primary Studies: Urine versus Cervical Samples for HR-HPV Detection (Table 2)

In high-risk HIV positive women, Kaoma *et al.* [49] showed an HR-HPV detection sensitivity of 84.8% (68.1 - 94.9) and specificity of 92.3% (83.0 - 97.5) using first void urine. Intan *et al.* [50] compared urine HR-HPV ReadyMix qPCR with cervical Cobas 6800 in 876 colposcopy referrals, showing urine sensitivity of 80.9% and specificity of 100% for HR-HPV detection. Lee *et al.* [51] evaluated the Cobas HPV test on urine in a screening based diagnostic validation (n = 67), reporting HPV16 sensitivity of 81.3%, HPV18 sensitivity of 100%, and other HR-HPV sensitivity of 96.4%, with specificities of 98.0%, 95.3%, and 100%, respectively. Vergara *et al.* [52] found that urine had a sensitivity of 82.7% (78.0 - 86.8) and specificity of 94.6% (90.9 - 97.1) for any HR-HPV detection in a screening population of 543 women. Tshomo *et al.* [53] reported urine sensitivity of 80% (67 - 90) and specificity of 61% (43 - 76) for 21 HPV types in a follow up cohort. Lim *et al.* [54] compared two assays on urine in 100 screening women: Roche cobas 4800 gave HPV16/18 sensitivity of 79.2% (57.9 - 92.9) and Abbott RealTime 81.8% (59.7 - 94.8), with 100% specificity for both. Combata *et al.* [55] showed urine sensitivity of 90.6% (87.0 - 94.0) for any HPV and 62% - 100% for type specific detection, with specificity of 74.1% (68.0 - 80.0) for any HPV and 96% - 99% for types 6/11/16/18. Tanzi *et al.* [56] found near perfect agreement in HIV positive women: urine sensitivity 98.6% (93.1 - 99.9) and specificity 97.4% (87.7 - 99.9) for HPV detection.

3.3.3. Primary Studies: Urine and Vaginal Self-Sampling versus Cervical Samples for HR-HPV Detection (Table 3)

Giubbi *et al.* [57] reported that for HR-HPV detection, urine had a sensitivity of 93.4% and specificity of 83.5%, while vaginal self-sampling achieved 99.1% sensitivity and 85.0% specificity ($\kappa = 0.773$ and 0.870 , respectively). Mizuno *et al.* [58] evaluated BD Onclarity in an abnormal cytology cohort ($n = 121$): urine sensitivity was 46.4% (36.0 - 57.1) and specificity 77.1% (60.2 - 88.5), whereas vaginal self-sampling gave 75.7% (65.7 - 85.6) sensitivity and 69.0% (52.2 - 85.7) specificity. Kuriakose *et al.* [59] compared urine directly with vaginal self-sampling without a cervical reference, reporting a urine sensitivity relative to vaginal of 57.9% (47.5 - 67.7) and specificity of 84.6% (66.4 - 93.8). Tranberg *et al.* [60] studied 150 women referred with ASC-US positive cytology: urine vs. vaginal self-sample gave a sensitivity of 59.1% (43.2 - 73.7) and specificity of 99.1% (94.9 - 99.7) for HR-HPV detection; urine vs. cervical samples gave 63.9% (46.2 - 79.2) sensitivity and 96.5% (91.3 - 99.0) specificity.

3.4. Quality Appraisal of the Included Diagnostic Studies Using the QUADAS-2 Style

To help interpret the diagnostic accuracy estimates we assessed the included primary studies using four QUADAS 2 domains: patient selection, index test, reference standard, and flow/timing. We did not apply formal scoring; instead, we summarize the main risk-of-bias and applicability concerns qualitatively.

3.5. Patient Selection

Many studies enrolled women from colposcopy referral cohorts with a high CIN2+ prevalence, including Van Keer *et al.* [24], Zhao *et al.* [28], Punyashthira *et al.* [32], Lorenzi *et al.* [29], and Cuzick *et al.* [15]. These referral-enriched samples may inflate sensitivity and limit specificity relative to true screening populations. By contrast, fewer studies were conducted in screening settings, such as Davies *et al.* [22], Xu *et al.* [23], Vergara *et al.* [52], and Stanczuk *et al.* [38], and these are more applicable to population-based screening. High-risk cohorts, including HIV-positive women in Kaoma *et al.* [49] and Tanzi *et al.* [56], further restrict generalizability. For example, in a screening population, Davies *et al.* reported urine sensitivity of 96.0% for CIN2+ and specificity of 85.2% [22], whereas in a referral cohort, Cuzick *et al.* found sensitivity of 88.3% but specificity of only 24.7% [15], illustrating the effect of disease enrichment on predictive performance. Among HIV-positive women, Kaoma *et al.* reported sensitivity of 84.8% and specificity of 92.3% for CIN2+ [28], while Tanzi *et al.* found nearly perfect agreement for overall HPV detection (sensitivity 98.6%, specificity 97.4%) [56]. In younger women (aged 19 - 25 years), Combata *et al.* found that first-void urine produced HPV prevalence estimates similar to cervical samples [55]. Overall, the large variation in CIN2+ prevalence across studies indicates substantial spectrum bias, so direct numerical comparisons should be interpreted cautiously.

3.6. Reference Standard and Verification Bias

Two main reference standards were used: clinician-collected cervical HPV DNA testing, as in [50], [51], and [54], and histologically confirmed CIN2+, as in [22], [26], [38], and [47]. Cervical HPV comparison mainly reflects assay agreement rather than clinical disease detection, which may overstate performance for CIN2+ detection. Where histology was used, many studies verified only HPV-positive or abnormal cytology cases, creating partial verification bias, particularly in referral cohorts such as Van Keer *et al.* [27] and Lorenzi *et al.* [29]. Only a few large studies, including Stanczuk *et al.* [38] and Xu *et al.* [23], applied colposcopy and biopsy to all participants and therefore avoided this bias.

3.7. Index Test and Assay Validation

Most studies used commercial PCR-based assays, including Cobas, Abbott, BD Onclarity, Anyplex, and GeneXpert, but these platforms were not always formally validated for urine or vaginal self-samples. Pre-analytical procedures also varied, including first-void versus random urine, preservation methods, and extraction kits. Assay selection and threshold setting strongly influence diagnostic performance. Commercial PCR-based assays generally show better and more consistent results than less standardized platforms. Van Keer *et al.* [25] found that the Abbott Alinity m HR-HPV assay on first-void urine achieved a relative sensitivity of 0.91 and relative specificity of 1.04 at the manufacturer's cut-off; after cut-off adjustment, performance improved to 0.96 and 1.00, respectively. Similar patterns were observed with the OncoPredict HPV QT assay in Latsuzbaia *et al.* [43], where sensitivity was already high but specificity improved after optimization. Cuschieri *et al.* [16] and Giubbi *et al.* [42] also showed that cut-off optimization improved the clinical performance of self-samples, particularly by restoring specificity toward the cervical benchmark. The meta-analysis by Cho *et al.* [14] further emphasized assay dependence, noting that some PCR-based assays showed relative sensitivity close to 1.00, whereas the overall pooled relative sensitivity for urine was 0.84. Regarding specimen type and target, Mathews *et al.* [46] suggested that mRNA assays may perform at least as well as DNA assays on self-collected vaginal samples, although evidence remains limited.

Pre-analytical conditions also have a substantial effect on urine HPV detection. First-void urine consistently outperforms random or midstream urine because it contains more exfoliated cervicovaginal material. Senkomago *et al.* [40] showed that initial-stream urine performed similarly to first-void urine, achieving 89.9% sensitivity for CIN2+, whereas midstream specimens were less informative. Davies *et al.* [33] demonstrated that a dedicated first-void device (Novosanis Collipee® 10 mL with urine conservation medium) improved sensitivity for CIN2+ to 90.3%, compared with 73.4% using a standard pot. Preservation and processing also matter: Kaoma *et al.* [49] used EDTA-preserved first-void urine and obtained strong performance in HIV-positive women. The tested urine fraction (pellet vs. supernatant) is another relevant variable; both may contain HPV DNA, but yield

depends on collection and processing methods. Overall, the evidence supports standardized first-void collection, prompt preservation, and validated extraction workflows as prerequisites for reliable urine-based HPV testing.

Agreement between self-collected and clinician-collected samples ranges from fair to excellent, depending on assay, population, and study design. The lowest agreement in this evidence set was $\kappa = 0.29$ [59] (Kuriakose *et al.*, 2020), while Tanzi *et al.* [56] reported near-perfect agreement for HPV detection in HIV-infected women ($\kappa = 0.96$). Most recent VALHUDES studies showed moderate to substantial agreement, e.g., $\kappa = 0.68 - 0.87$ for Cobas assays [24] and $\kappa = 0.68 - 0.87$ for Alinity m HR-HPV [44]. Importantly, agreement statistics alone do not always reflect clinical usefulness; some studies showed only moderate κ while still achieving non-inferior CIN2+ detection [22] [23].

Studies using the same assay across urine, vaginal, and cervical samples, such as Latsuzbaia *et al.* [43], and Giubbi *et al.* [42], have stronger internal validity. In contrast, studies using different assays for urine and cervical samples, such as [50], may reflect assay disagreement as well as true sample differences.

3.8. Flow and Timing

Most studies were cross-sectional and collected paired urine, vaginal, and cervical samples at the same visit, which is appropriate for diagnostic accuracy assessment. However, blinding of the reference standard to index test results was rarely reported, and the interval between sampling and biopsy was not always stated. Overall, the evidence is limited by referral-enriched cohorts, mixed reference standards, and partial verification. Accordingly, studies with screening populations, histology applied to all participants, and the same assay across specimen types provide the most robust estimates, whereas the reported ranges in sensitivity and specificity, including urine sensitivity for CIN2+ from 63% to 96%, should be interpreted in light of these limitations.

4. Discussion

This narrative review synthesizes endpoint-specific evidence on urine-based and self-collected vaginal HPV testing compared with clinician-collected cervical samples for CIN2+/CIN3+, HSIL+, and HR-HPV detection. Across meta-analyses using histology as the reference, urine HPV testing showed pooled sensitivities for CIN2+ of about 74% - 83% and specificities of 51% - 58% [17]-[19], whereas when the endpoint was cervical HR-HPV detection rather than disease, pooled urine specificity increased to around 90%. First-void urine and appropriate preservation consistently improved performance relative to random or mid-stream urine [13]. For CIN2+/CIN3+, vaginal self-sampling generally demonstrated higher pooled sensitivities (often 92% - 98% for >CIN2+ lesions), but specificities ranged more widely (approximately 63% - 80%) and depended strongly on assay and cut-off [7] [16] [21]. In head-to-head comparisons within the same studies, vaginal self-samples were usually more sensitive than urine for CIN2+/CIN3+ detection, but

this gap narrowed in VALHUDES-type studies once cut-offs were optimized [16] [34] [35] [38]. For HSIL+, evidence was sparse: one colposcopy-based study reported almost perfect urine accuracy (sensitivity 97.8%, specificity 100%), while no robust HSIL-only estimates were available for vaginal sampling [47]. For HPV detection, urine typically achieved sensitivities around 75% - 85% and specificities near 90%, whereas vaginal self-sampling often exceeded 90% sensitivity with specificities around 80% - 85% [18] [48] [51]-[53] [55]-[57] [59]. Taken together, these endpoint-specific data suggest that urine-based HPV testing is a viable option for women who decline cervical or vaginal sampling, provided that first-void collection, validated PCR-based assays, and optimized cut-offs are implemented, while vaginal self-sampling remains the more sensitive method for detecting CIN2+/CIN3+ and is already endorsed by WHO.

The substantial variability in reported sensitivity and specificity can be explained by differences in endpoint, assay technology, pre-analytical procedures, population, and reference standard. PCR-based assays (e.g., GP5+/6+, Cobas, Alinity, Onclarity, OncoPredict) tend to deliver higher and more stable sensitivity for both CIN2+/CIN3+ and HR-HPV detection than signal-based methods [7] [22] [24] [26] [50] [58]. However, applying manufacturer cut-offs derived from cervical samples directly to urine or vaginal specimens often reduces specificity for CIN2+/CIN3+ and, in some settings, for HR-HPV [16] [25] [42] [43]. The VALHUDES initiative has demonstrated that cut-off optimization for self-samples can restore specificity to levels non-inferior to clinician-collected samples without compromising sensitivity [16] [25] [42]-[44]. Pre-analytical variation in urine collection is another major driver: first-void urine, which contains more exfoliated cervicovaginal cells and cell-free DNA, consistently improves both HR-HPV and CIN2+/CIN3+ detection compared with random or mid-stream urine [40]. Davies *et al.* [33] showed that a dedicated first-void device almost doubled CIN2+ sensitivity relative to a standard container, while preservation buffers such as EDTA or UCM (urine conservation medium) reduced DNA degradation and improved concordance [33]. The urine fraction tested (pellet vs. supernatant vs. whole) also influenced HR-HPV detection [40].

Population disease prevalence and spectrum also shape endpoint-specific accuracy. Referral cohorts with high CIN2+ prevalence tend to show high sensitivity but low specificity for CIN2+/CIN3+ because of spectrum and verification bias, whereas screening populations provide more realistic specificity estimates and more generalizable CIN2+/CIN3+ performance. High-risk groups, notably women living with HIV, often show excellent HR-HPV detection using urine, with near-perfect agreement between urine and cervical samples in some studies [49] [56]. Differences in reference standards further contribute to heterogeneity. When cervical HR-HPV positivity is used as the reference, specificity of urine and vaginal samples appears higher because the endpoint is viral infection, measured by a relatively objective molecular test. In contrast, histologically confirmed CIN2+/CIN3+ is clinically more relevant but depends on biopsy sampling and

subjective pathology interpretation, so differences in pathology practice (biopsy protocols, diagnostic thresholds) make CIN2+/CIN3+ a more variable benchmark across studies. Geographic and demographic diversity, including HPV genotype distribution and co-infections, may also affect both HR-HPV and CIN2+/CIN3+ performance, with some studies from sub-Saharan Africa and Asia reporting patterns distinct from those in Europe or South America [49] [53] [55] [56].

5. Clinical Implications of Endpoint-Specific Findings

For screening programs, endpoint-specific interpretation is crucial. When the primary goal is detection of CIN2+/CIN3+, vaginal self-sampling provides the most robust evidence base, with high sensitivity and acceptable specificity when PCR-based assays and optimized cut-offs are used [7] [16] [34]-[36] [38] [42] [43] [46]. For urine, CIN2+/CIN3+ sensitivity is generally moderate-to-high but specificity around 50% - 60% in many referral populations [15] [17]-[19] [29] [30] [37] [39], so urine HPV testing is best viewed as a first-line, highly acceptable option that requires triage (e.g., repeat testing, cytology, or direct colposcopy) to mitigate false positives. In high-prevalence or high-risk settings such as HIV-positive cohorts, the positive predictive value for CIN2+/CIN3+ may be adequate even with modest specificity, but programs should still prioritize first-void collection and validated PCR assays. When the clinical decision focuses on HR-HPV infection (e.g., surveillance, post-treatment follow-up, or vaccine impact monitoring), both urine and vaginal self-samples show high agreement with cervical HR-HPV, with vaginal sampling generally achieving the highest sensitivity and urine often providing very high specificity [13] [18] [21] [31] [48] [50]-[52] [54]-[57].

Where both self-sampling routes are available, vaginal self-sampling remains the preferred method for primary detection of CIN2+/CIN3+ because of its higher sensitivity, while urine offers a fully non-invasive alternative for women who decline vaginal sampling or pelvic examinations. In low-resource settings, urine collection with a simple first-void device and ambient-temperature stabilization may be logistically simpler than vaginal swabs that require liquid media or cold chain. A key clinical lesson across endpoints is that manufacturer cut-offs validated for cervical samples cannot be assumed valid for self-samples; laboratories offering HR-HPV or CIN2+/CIN3+ detection on urine or vaginal specimens must establish assay-specific thresholds through appropriate validation, following frameworks such as VALHUDES. Acceptability data, although not the primary focus here, indicate that many women prefer urine over vaginal or cervical sampling, suggesting that offering both options could increase overall screening coverage and help reach never-screened populations.

6. Limitations and Future Research

Several limitations affect the strength and generalizability of these endpoint-specific conclusions. The search was limited to PubMed and a specific keyword set, so relevant studies in other databases may have been missed despite manual ref-

erence screening. Because of substantial heterogeneity in endpoints, assays, cut-offs, urine collection methods, reference standards, and populations, a formal quantitative meta-analysis was not undertaken, and many primary studies did not report predictive values (PPV and NPV), limiting comparison of clinical utility across CIN2+/CIN3+ and HR-HPV endpoints. There is no universally accepted standard for urine collection (first-void volume, device, preservation, transport, fraction to test), complicating cross-study comparisons and preventing firm “best practice” recommendations; future work should adopt harmonized protocols. Evidence on longitudinal endpoints—such as the negative predictive value of urine-based testing over time or its impact on cervical cancer incidence—is scarce. Moreover, most studies originate from high-income settings with established screening infrastructure, so performance in truly low-resource environments remains uncertain. Finally, publication bias cannot be excluded, as positive or higher-accuracy studies may be over-represented.

Priorities for future research include prospective screening trials that compare urine-based HPV testing and vaginal self-sampling with standard care, with long-term follow-up for CIN2+/CIN3+ and cancer; implementation and cost-effectiveness studies in low-resource and remote settings; and consensus-driven standardization of urine collection and processing protocols. Assay validation studies should explicitly address cut-off optimization for each endpoint and compare DNA- and mRNA-based assays on self-samples. Triage strategies tailored to urine-positive or vaginal-positive women warrant evaluation to improve specificity for CIN2+/CIN3+ while retaining high sensitivity. Finally, mixed-methods research on acceptability and preferences, especially in culturally diverse and high-burden settings, will inform how best to offer and position urine and vaginal self-sampling within integrated screening programs.

7. Conclusion

Self-collected vaginal and urine samples both show clinically meaningful diagnostic performance for cervical cancer prevention, but their strengths differ by endpoint. Vaginal self-sampling, when combined with validated PCR-based assays and optimized cut-offs, achieves high sensitivity and acceptable specificity for CIN2+/CIN3+ and is therefore the best-supported option for primary screening, in line with current WHO recommendations. Urine-based HPV testing offers a fully non-invasive, highly acceptable alternative that provides moderate-to-high sensitivity for CIN2+/CIN3+ and high accuracy for HR-HPV detection, particularly when first-void collection, appropriate preservation, and assay-specific thresholds are used; it is especially valuable for women who decline pelvic or vaginal examinations and for hard-to-reach populations. Across all endpoints, reliable use of self-sampling requires standardized collection protocols, rigorous assay validation on self-samples (rather than simple transfer of cervical cut-offs), and context-specific triage strategies to manage false positives while preserving sensitivity. Programs that offer women a choice between vaginal and urine self-sampling, and

tailor implementation to local resources and population risk, are likely to maximize screening participation and contribute meaningfully to global efforts to eliminate cervical cancer as a public health problem.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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