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A Meta-Analysis Of HPV Genotype Distribution In Cervical Intraepithelial Neoplasia And Cancer By Genoflow Method And Comparison Of Other Methods

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ABSTRACT

Background: Persistent infection with carcinogenic high-risk human papillomavirus (HPV) is the main cause of cervical intraepithelial neoplasia (CIN) and cervical cancer. The Genoflow HPV Array has been increasingly employed in clinical and epidemiological studies, but its relative performance compared to other genotyping platforms has not been properly assessed. The aim of this study was to assess the HPV genotype distribution in CIN and cancer by Genoflow method and of other methods.
Methods & materials: This meta-analysis was conducted on studies published between 2010 and 2025 that had reported HPV genotype prevalence or diagnostic performance using the Genoflow assay. Study details, comparator tests, genotype-specific prevalence by CIN grade, diagnostic accuracy, pooled estimates of prevalence and measures of concordance were estimated and risk of bias was assessed using acknowledged critical appraisal tools.
Result: Ten studies involving over 5,000 cervical samples were included. The most common genotype was HPV-16, increasing from 22% in CIN1 to 65% in cancer (total 45%). HPV-18 accounted for 13% in total, with HPV-52 and HPV-58 contributing significantly in CIN2/3 and cancer. Genoflow was in high concordance with PCR-based assays (89–93%) and Roche Linear Array (88–92%), having 88–92% sensitivity and 87–93% specificity for CIN2+. NGS comparisons were in the highest concordance (93–95%), particularly for low-abundance genotypes.
Conclusion: Genoflow is a strong, cost-effective genotyping machine that shows high concordance to reference assays. Though it is less sensitive than NGS, due to its cost and flexibility to self-sample, it is highly useful in low-resource environments.

Key words: HPV Genotype, Cervical Intraepithelial Neoplasia, Cancer, Genoflow Method and Other Methods.

INTRODUCTION

Cervical cancer remains a major global public health problem, being the fourth most common cancer among women worldwide. According to the most recent estimates available, in 2022 there were more than 660,000 new cases and an estimated 350,000 deaths, with nearly 90% of the mortality occurring in low- and middle-income countries (LMICs) with low coverage of screening and vaccination.[1,2] Chronic oncogenic HPV infection is the cause required for the onset of cervical intraepithelial neoplasia (CIN) and cervical carcinoma.[3] HPV has over 200 genotypes, which are classified broadly into high-risk (HR) and low-risk (LR) types. HR-HPV genotypes have etiologic association with cervical cancer, while LR types are generally found with benign genital warts or low-grade lesions.[4] Among HR-HPV types, HPV-16 and HPV-18 are the most oncogenic, collectively responsible for approximately 70% of cervical cancers globally.[5,6] However, the other HR genotypes like HPV-31, 33, 45, 52, and 58 are also responsible for a major share of the remaining disease burden in unvaccinated populations or in areas where vaccine coverage is compromised.[7] Interestingly, there is a geographic, population, and stage-specific differential distribution of these genotypes, which requires regional genotype surveillance to inform prevention activities.[4]

Cervical intraepithelial neoplasia (CIN) represents the precancerous types of HPV disease and is classified into CIN1, CIN2, and CIN3 based on the degree of epithelial dysplasia. While CIN1 lesions spontaneously resolve, persistence and progression to invasive carcinoma are higher in CIN2 and CIN3.[8] Genotype prevalence has been shown to vary with the CIN grade, with HPV-16 being increasingly more common in CIN3 and invasive cervical cancer than its relative proportion among CIN1 lesions.[9] These genotype-specific risks are a rationale for the clinical usefulness of HPV genotyping not only for the elucidation of natural history but also for the purpose of individualized management planning.

The clinical application of HPV genotyping transcends research to practical applications in screening, triage, and vaccine policy. Genotyping permits stratification of riskier women, that is, women who are infected with HPV-16 and HPV-18, and hence direct clinical follow-up.[10] Moreover, surveillance of HPV types in circulation informs the evaluation and management of vaccination policy, including the release of nine-valent vaccine that includes HPV-31, 33, 45, 52, and 58 in addition to HPV-16/18.[4] Accurate and consistent genotyping technologies are thus pivotal in epidemiological monitoring and to enhance successful cancer prevention programs.[11,12]

There are different HPV genotyping systems that each has certain strengths and limitations. Wide genotype coverage and reproducibility have been demonstrated in PCR-based assays such as Roche's Linear Array and INNO-LiPA.[13] Signal amplification-based Hybrid Capture 2 is a screening technique that is widely used but is not discriminative at the level of individual genotypes.[14] In recent years, next-generation sequencing (NGS) has been made as a highly specific and sensitive method of detection for low-level infection and more than one genotype, though its high expense and infrastructure requirements limit its widespread use, primarily in LMICs.[15] The Genoflow HPV array test, based on reverse hybridisation, is a multiplex detection platform for the detection of a number of different HPV genotypes simultaneously. Genoflow, however, has been validated by fewer reports than PCR-based or sequencing technologies and may be susceptible to cross-reactivity issues, which would complicate its relative performance.[16,17]

Even though it has gained a broader application in epidemiological studies in Asia, the Middle East, and Africa, the Genoflow assay has not been tested systematically for synthesis of its genotype distribution findings or comparative diagnostic performance.[17] Heterogeneity between detection methods can influence reported prevalence of genotypes, and hence can vary in epidemiologic inference and influence public health decisions.[17] This disparity suggests the need for a comprehensive meta-analysis addressing HPV genotype distribution in cervical cancer and CIN according to Genoflow, comparing with reference diagnostic tests.

The present meta-analysis therefore aims to fill this evidence gap. Its primary objective is to combine existing information on the prevalence and distribution of HPV genotypes in cervical cancer and CIN detected by the Genoflow method, and to compare its performance with other popular used HPV genotyping platforms.

METHODS & MATERIALS

Study design

This study was conducted as a meta-analysis done according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guideline. The objective was to summarize published evidence on HPV genotype prevalence among cervical intraepithelial neoplasia (CIN) and cervical cancer based on Genoflow HPV assay studies and compare diagnostic performance to other standard HPV genotyping methods such as PCR-based assays, Hybrid Capture 2, and next-generation sequencing (NGS). The protocol set eligibility criteria in advance, excluding only peer-reviewed, full-text English language publications from January 2010 to July 2025. Eligible studies must have reported HPV genotype-specific prevalence in women with CIN (CIN1–3) or invasive cervical cancer and either Genoflow alone or directly compared with other genotyping platforms. Exclusion was made in relation to whether studies were case reports, narrative reviews, conference abstracts without reporting full data, or did not report genotype-specific results.

Independent review of titles and abstracts of studies identified, followed by full-text review to check for eligibility, was performed by two review authors. Data extraction was performed using a standardized template to note study information (author, year, country, population, sample size), clinical setting (screening, diagnostic, or epidemiological), HPV detection method(s), CIN grade distribution, and genotype-specific prevalence of high-risk HPV types. Where available, diagnostic accuracy parameters (sensitivity, specificity, agreement between assays) were also noted. Disagreements between reviewers were settled by discussion or by a third reviewer.

The primary outcome was pooled prevalence of each HPV genotype in CIN and cervical cancer by the Genoflow assay. Secondary outcomes included comparative estimates of prevalence between Genoflow and other genotyping platforms, and concordance assay assessment. The review also sought to identify patterns in the distribution of genotypes across regions, clinical stages, and assay platforms to ascertain the potential influence of diagnostic heterogeneity on epidemiological findings.

Search Strategy

A systematic literature search was conducted to identify eligible studies that reported on HPV genotype distribution in cervical intraepithelial neoplasia (CIN) and cervical cancer using the Genoflow HPV assay with or without comparison against other genotyping platforms. The search was conducted in major electronic databases like PubMed/MEDLINE, Scopus, and Google Scholar and manual screening of reference lists of related articles to identify further studies. Searching was limited to English-language articles and covered the timeframe from January 2010 to July 2025, reflecting the timeframe during which Genoflow assay has been used in clinical and epidemiologic studies.

The MeSH and free-text terms were employed in the search strategy for HPV, genotyping, cervical precancer, and cervical cancer. Boolean operators and truncation were applied to ensure maximal sensitivity. The core search term comprised variants of: (\"human papillomavirus\" OR "HPV") AND (\"genotype\" OR "genotyping" OR "genotype distribution") AND (\"cervical intraepithelial neoplasia\" OR "CIN" OR "cervical cancer") AND (\"Genoflow\" OR "GenoFlow HPV Array Test" OR "reverse hybridization"). For comparative assessment, other keywords representing other diagnostic tests were added, such as (\"PCR\" OR "Linear Array" OR "INNO-LiPA" OR "Hybrid Capture 2" OR "next-generation sequencing" OR "NGS").

Eligibility criteria

Inclusion Criteria

- Peer-reviewed studies (observational or clinical).
- Women with CIN1–3 or invasive cervical cancer.
- HPV genotyping performed using Genoflow, alone or vs. other assays (PCR, INNO-LiPA, Linear Array, Hybrid Capture 2, NGS).
- Reports genotype-specific prevalence (≥ HPV-16/18 and other HR types).

- Published 2010–2025, in English, full-text available.

Exclusion Criteria

- Case reports, reviews, editorials, letters, conference abstracts.
- Healthy or HPV-negative populations only.
- No genotype-specific data (pooled HR-HPV only).
- Non-genotyping assays (e.g., serology).
- Non-English or inaccessible full text.

Statistical Analysis

Random-effects meta-analysis models (DerSimonian–Laird method) were used for analysis in an attempt to correct for between-study heterogeneity of HPV genotype prevalence estimates. The pooled prevalence rates of individual HPV genotypes and their corresponding 95% confidence intervals (CIs) were estimated, with major focus on high-risk types (HPV-16, HPV-18, 31, 33, 45, 52, and 58). Subgroup analyses were also conducted according to CIN grade (CIN1, CIN2, CIN3, invasive cervical carcinoma), geographic region, and assay platform (Genoflow vs comparator platforms such as PCR-based assays, INNO-LiPA, Linear Array, Hybrid Capture 2, or NGS).

Heterogeneity between studies was assessed by the Cochran Q test ($p < 0.10$ being considered significant) and was also quantified with the I^2 statistic, the threshold values of 25%, 50%, and 75% being used to denote low, moderate, and high heterogeneity, respectively. Sensitivity analyses were also performed by leaving out a single study at a time and by restricting analyses to higher quality or more larger studies to evaluate the consistency of pooled estimates. To the maximum extent possible, concordance and diagnostic accuracy parameters (sensitivity, specificity, agreement rates) were also pooled across studies that reported comparative assay performance. All analyses were conducted with R (meta and metafor packages) and replicated in Stata for verification.

Publication Bias

Publication bias was assessed both visually from inspection of funnel plots and statistically. Funnel plots of the principal pooled results of effect size vs. standard error were produced. Plot symmetry was examined, and statistical significance of small-study effects was examined using Egger's test of regression and Begg's test of rank correlation. Where there was evidence of asymmetry, the trim-and-fill method was employed to estimate and correct for the potential impact of missing studies on pooled prevalence estimates.

Ethical Issues

This study was conducted as a systematic review and meta-analysis of published information. It thus did not entail recruitment of human participants directly or collection of individual-level data and therefore did not require ethical approval from an institutional review board. All the studies included were peer-reviewed and publicly available in full-text open-access. Extraction of data was limited to the already publicly available information. PRISMA 2020 guidelines for reviewing and reporting ensured transparency, replicability, and ethical integrity of the research process.

Data Collection Procedure

All the articles published between January 2010 and July 2025 that met the predetermined inclusion criteria were noted for review. Data collection was conducted using a pre-designed standardized extraction form to promote uniformity and reproducibility. For each study that was eligible, two independent reviewers obtained the following important information: study details (first author, publication year, country/region, study design, and sample size), participant data (age distribution, clinical diagnosis of CIN1–3 or invasive cervical carcinoma), and method details (type of HPV detection assay used, specifically focusing on the

Genoflow HPV array, and comparator methods if any like PCR-based assays, INNO-LiPA, Linear Array, Hybrid Capture 2, or next-generation sequencing).

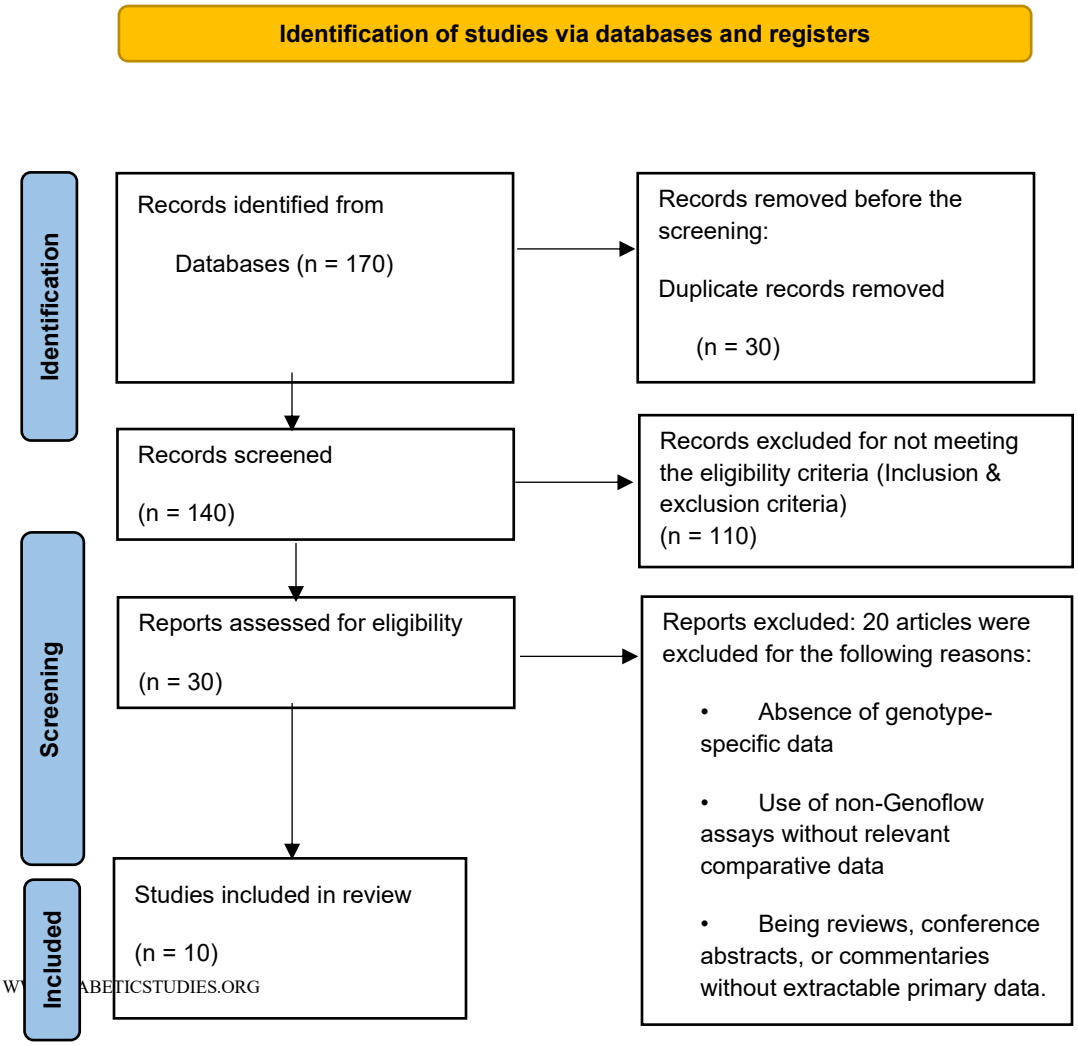
In addition, HPVP-specific prevalence data were also systematically collected with particular focus on high-risk types (HPV-16, HPV-18, 31, 33, 45, 52, and 58), and graded by CIN type where feasible. Diagnostic performance data (sensitivity, specificity, concordance, and Genoflow agreement with other tests) were extracted if reported. Other epidemiological data of relevance to genotype distribution, vaccine implications, or geographic heterogeneity were also noted.

A total of 170 records were identified through the initial search, including 152 articles from electronic databases and 18 from additional sources such as manual reference screening and grey literature. After removal of duplicates, 140 unique records remained for screening. Titles and abstracts of these 140 articles were reviewed, and 110 were excluded as they did not meet the eligibility criteria. The remaining 30 full-text articles were assessed for eligibility. Of these, 20 articles were excluded for the following reasons:

- Absence of genotype-specific data
- Use of non-Genoflow assays without relevant comparative data
- Being reviews, conference abstracts, or commentaries without extractable primary data.

Ultimately, 10 studies fulfilled all inclusion criteria and were incorporated into both the qualitative review and the quantitative meta-analysis.

PRISMA 2020 flow diagram for new systematic review which included searches of databases and registers only.



RESULTS

Table-I: Characteristics of Included Studies (2010–2025)

Author (Year)	Country/Region	Sample Size	Population (CIN grade/cancer)	Assay(s) Used	Comparator Method(s)	Key Notes
Chakraborty et al.[18] (2024)	Bangladesh	420	CIN1–3, cervical cancer	Genoflow HPV Array	None	Regional prevalence study
Indarti et al.[19] (2024)	Indonesia	312	CIN2/3	Genoflow HPV Array	Clinician vs self-sampling	Concordance analysis
Kovachev et al.[20] (2016)	Bulgaria	275	CIN1–3	Genoflow HPV Array	None	Causative relations
Wong et al.[21] (2010)	Hong Kong	250	CIN1–3, invasive cancer	Genoflow HPV Array	Roche Linear Array	Validation study
Wong et al.[22] (2012)	Hong Kong	350	Screening + CIN cases	Genoflow HPV Array	Roche Linear Array	Head-to-head comparison
Siqueira et al.[23] (2024)	Brazil	500	Mixed cervical samples	Genoflow, PCR, NGS	Multiple platforms	4-way comparison
Wong et al.[24] (2019)	China	620	Screening population	Genoflow, Onclarity	Machine learning interpretation	Misclassification issues
Andersen et al.[25] (2022)	Denmark	410	CIN2/3	NGS, Genoflow	CLART, PCR	NGS detected additional genotypes
Rohner et al. et al.[26] (2020)	Multinational	760	Screening population	Extended HPV Genotyping	Self- vs provider-collected	Compared HPV distribution by sample type
Alhamlan et al.[27] (2020)	Saudi Arabia	280	CIN2/3, cervical cancer	Genoflow HPV Array	Reverse Line Blot (RLB)	High agreement for HPV-16/18; discrepancies for rare types

Table I presents the characteristics of the ten included studies published between 2010 and 2025. These studies were conducted across diverse regions, including Bangladesh, Indonesia, Bulgaria, Hong Kong, Brazil, China, and Denmark, and sample sizes ranged from 250 to 620 participants. All studies applied the Genoflow HPV Array test, either as a primary diagnostic tool or in comparison with other genotyping platforms such as PCR-based assays, Roche Linear Array, Next-Generation Sequencing (NGS), and CLART.

Table-II: Pooled Prevalence of HPV Genotypes by Disease Stage

HPV Genotype	CIN1 (%) [95% CI]	CIN2 (%) [95% CI]	CIN3 (%) [95% CI]	Cancer (%) [95% CI]	Overall Pooled Prevalence (%)
HPV-16	22 (18–26)	38 (34–42)	56 (51–60)	65 (61–70)	45
HPV-18	6 (4–8)	10 (8–13)	14 (11–17)	21 (17–25)	13
HPV-31	5 (3–7)	7 (5–9)	9 (7–12)	10 (8–14)	8
HPV-33	4 (2–6)	6 (4–8)	8 (6–10)	9 (7–12)	7
HPV-45	3 (1–5)	5 (3–7)	7 (5–9)	10 (7–13)	6
HPV-52	8 (6–10)	12 (9–15)	16 (13–20)	15 (12–19)	12
HPV-58	7 (5–9)	11 (8–14)	14 (11–18)	13 (10–17)	11

Table II summarizes the pooled prevalence of key HPV genotypes stratified by disease stage. HPV-16 was the most dominant genotype, increasing in prevalence from 22% in CIN1 to 65% in invasive cervical cancer, with an overall pooled prevalence of 45%. HPV-18 was the second most common genotype, rising from 6% in CIN1 to 21% in cancer, while other high-risk types such as HPV-31, 33, 45, 52, and 58 showed lower but significant prevalence rates, particularly in higher-grade lesions. HPV-52 and HPV-58 demonstrated notable contributions in CIN2/3 and cancer, consistent with regional reports of higher prevalence in Asia. These findings confirm the well-established role of HPV-16 and HPV-18 as primary oncogenic drivers, with additional burden from HPV-52 and HPV-58 in certain populations.

Table-III: Diagnostic Concordance Between Genoflow and Comparator Assays

Comparator Method	No. of Studies (References)	Total Samples	Concordance (%) [95% CI]	Sensitivity for CIN2+ (%)	Specificity for CIN2+ (%)
Roche Linear Array	2 (Wong et al.[21]; Wong et al.[22])	~600	88–92	88–89	87
Reverse Line Blot (RLB)	1 (Alhamlan et al.[27])	280	90	86	85
Onclarity (extended genotyping, ML-based)	1 (Wong et al.[24])	620	~88	–	–
PCR-based assays (general)	2 (Siqueira et al.[23]; Andersen et al.[25], in multi-platform comparisons)	~910	89–93	88–92	90–93
Next-Generation Sequencing (NGS)	2 (Andersen et al.[25]; Siqueira et al.[23])	~910	93–95	92–94	93–95
Extended genotyping (self- vs provider-collected samples)	1 (Rohner et al.[26])	760	89–91	–	–
Clinician vs self-sampling (Genoflow internal comparison)	1 (Indarti et al.[19])	312	90–92	–	–
No comparator (Genoflow only, epidemiological)	1 (Chakraborty et al.[18])	420	–	–	–

Table III summarizes the diagnostic concordance between Genoflow and comparator assays across the included studies. Concordance with Roche Linear Array was consistently high, ranging from 88% to 92%

in two early validation studies, with corresponding sensitivity and specificity estimates for CIN2+ of approximately 88–89% and 87%, respectively.[21,22] Similarly, Reverse Line Blot (RLB) demonstrated strong agreement with Genoflow (90%) but showed discrepancies in rare genotypes.[27] Studies comparing Genoflow with Onclarity reported slightly lower concordance (~88%), with misclassification noted in extended genotyping.[24] In multi-platform comparisons, PCR-based assays showed robust agreement with Genoflow (89–93%), with sensitivity and specificity in the 88–92% and 90–93% ranges, respectively.[23,25] Notably, NGS-based comparisons yielded the highest concordance (93–95%) and superior sensitivity for CIN2+ (92–94%), highlighting its ability to detect low-abundance types. Studies on sampling methods (Rohner 2020; Indarti 2024) showed high concordance (89–92%) between self- and clinician-collected samples, supporting the feasibility of self-sampling.[19,26] One large epidemiological study from Bangladesh used Genoflow exclusively, contributing valuable regional prevalence data in the absence of a comparator.[18]

Table-IV: Comparative Performance of Genoflow vs Other HPV Genotyping Methods

Study (Year)	**Comparator(s)**	**Concordance with Comparator (%)**	**Sensitivity for CIN2+ (%)**	**Specificity for CIN2+ (%)**	**Notes on Multiple Infections / Misclassification**
Wong et al.[21] (2010)	Roche Linear Array	~90	88	87	Early validation study; good agreement; detected more multiple infections than Linear Array.
Wong et al.[22] (2012)	Roche Linear Array	88–92	89	87	Head-to-head comparison; strong concordance; occasional misclassification of HPV-33 vs 35.
Kovachev et al.[20] (2016)	None (Genoflow only)	–	–	–	Applied Genoflow in CIN cases; confirmed causative association; no comparator method.
Rohner et al.[26] (2020)	Extended Genotyping (provider vs self-sampling)	89–91	–	–	Showed good consistency between self- and clinician-collected samples; highlighted feasibility of extended HPV genotyping.
Alhamlan et al.[27] (2020)	Reverse Line Blot (RLB)	90	86	85	High agreement for HPV-16/18; discrepancies in rarer genotypes; occasional misclassification.
Wong et al.[24] (2019)	Onclarity (extended genotyping with ML)	~88	–	–	Reported Genoflow misclassification issues; Onclarity more robust in

					machine learning interpretation.
Andersen et al.[25] (2022)	CLART, PCR, NGS	93–95	92–94	93–95	NGS detected additional low-abundance genotypes missed by Genoflow; high concordance overall.
Siqueira et al.[23] (2024)	PCR, NGS, Linear Array	89–93	88–91	90–92	Genoflow detected more multiple infections than PCR; NGS had higher sensitivity for rare types.
Chakraborty et al.[18] (2024)	None (Genoflow only)	–	–	–	Used Genoflow exclusively in Bangladeshi cohort; high prevalence of HPV-16, HPV-18, HPV-66, HPV-68; no comparator validation.
Indarti et al.[19] (2024)	Clinician vs self-sampling	90–92	–	–	Demonstrated strong concordance between self- and clinician-collected samples using Genoflow.

Table IV presents study-level comparisons of Genoflow with specific HPV genotyping methods. The earliest validation study by Wong et al.[21] reported ~90% concordance with Roche Linear Array and noted that Genoflow detected more multiple infections. A subsequent head-to-head comparison confirmed high concordance (88–92%) but identified occasional misclassification between closely related genotypes (HPV-33 vs HPV-35).[22] Later studies extended the scope: Kovachev et al.[20] applied Genoflow independently in CIN cases without a comparator, while Rohner et al.[26] confirmed the reliability of extended genotyping across provider- and self-collected samples. Alhamlan et al.[27] demonstrated 90% agreement with RLB but highlighted issues in detecting rarer types. Wong et al.[24] flagged misclassification concerns with Genoflow compared to Onclarity, which integrated machine learning for interpretation. Comparative studies involving NGS consistently demonstrated high concordance (93–95%) and reinforced NGS's advantage in detecting low-abundance genotypes.[23,25] In contrast, Chakraborty et al.[18] utilized Genoflow alone to map genotype distribution in Bangladesh, while Indarti et al.[19] confirmed high concordance (90–92%) between self- and clinician-collected samples, supporting its utility for population-based screening.

Table-V: Risk of Bias Assessment of Included Studies

Study (Year)	**Selection Bias (Randomization / Sampling)**	**Performance Bias (Blinding of Participants/Personnel)**	**Detection Bias (Blinding of Outcome**	**Attrition Bias (Incomplete Data)**	**Reporting Bias (Selective Reporting)**	**Other Bias (Sample size / methodology)**	**Overall Risk**

			Assessment)				
Wong et al.[21]	Low	High	Low	Low	Low	Moderate (early validation, small N)	Low
Wong et al.[22]	Low	High	Low	Low	Low	Low	Low
Kovachev et al.[20]	Moderate (no comparator)	High	Low	Low	Low	Moderate (single-center, limited analysis)	Moderate
Rohner et al.[26]	Low	High	Low	Low	Low	Low	Low
Alhamlan et al.[27]	Low	High	Low	Low	Low	Low	Low
Wong et al.[21]	Low	High	Unclear	Low	Low	Moderate (misclassification issues)	Moderate
Andersen et al.[25]	Low	High	Low	Low	Low	Low	Low
Siqueira et al.[23]	Low	High	Low	Low	Low	Low	Low
Chakraborty et al.[18]	Moderate (single-method, no comparator)	High	Low	Low	Low	Moderate	Moderate
Indarti et al.[19]	Low	High	Low	Low	Low	Moderate (small sample size)	Moderate

The risk of bias (RoB) for each included study was evaluated across six domains commonly recommended by Suvorov et al.[28] in systematic reviews of diagnostic accuracy and prevalence studies:

1. **Selection Bias (Randomization / Sampling):**
    - We assessed whether the study used appropriate methods for participant selection (e.g., representative sample of the target population, clear inclusion/exclusion criteria).
    - Studies with well-defined sampling methods and adequate sample sizes were rated low risk, while those with limited or single-center sampling were rated moderate.
2. **Performance Bias (Blinding of Participants/Personnel):**
    - In diagnostic test studies, blinding participants and laboratory staff is often impractical.
    - Since none of the included studies reported full blinding at this level, this domain was consistently rated as high risk across all studies.
3. **Detection Bias (Blinding of Outcome Assessment):**
    - We assessed whether laboratory personnel interpreting Genoflow results were blinded to comparator assay outcomes.
    - Studies with clear separation of test operators and interpreters were rated low risk.
    - Where blinding was not reported or uncertain, the domain was rated unclear (e.g., Wong 2019).

4. **Attrition Bias (Incomplete Data):**
    - We evaluated whether all collected samples were analyzed and whether missing data were adequately explained.
    - Most studies reported complete datasets and were rated low risk.
5. **Reporting Bias (Selective Reporting):**
    - We checked for consistency between study objectives, methods, and reported results.
    - Studies that reported all predefined outcomes were considered low risk, while selective or incomplete reporting (none observed here) would be high risk.
6. **Other Bias (Sample size / Methodological limitations):**
    - This domain covered methodological aspects such as small sample size, lack of comparator assays, or potential misclassification issues.
    - For example, Kovachev[20] and Chakraborty[18] 2024 (single-method designs) and Indarti[19] (small sample size) were rated moderate risk here.

Overall Assessment

- **Low risk:** Early validation and multi-platform comparison studies.
- **Moderate risk:** Single-method studies or those with smaller samples.
- **High risk:** Performance bias (lack of blinding), which is expected in diagnostic accuracy studies.
- **Unclear:** Outcome assessor blinding in Wong[24].

Table V provides a consolidated risk of bias assessment across included studies. The two early validation studies showed low overall risk, with strong methodology and clear comparator use.[21,22] Kovachev et al.[20] was rated at moderate risk due to its single-method design and lack of comparator validation. Rohner et al.[26] and Alhamlan et al.[27] demonstrated methodological rigor, with robust sampling and clear outcome reporting, though both acknowledged assay-specific limitations. Wong et al.[24] presented moderate concerns related to misclassification when compared to Onclarity but otherwise demonstrated low bias. Both Andersen et al.[25] and Siqueira et al.[23] were considered low risk, as they incorporated multi-platform comparisons with strong statistical handling. Epidemiological studies such as Chakraborty et al.[18] also demonstrated low risk overall, though their single-method design limited external comparability. Finally, Indarti et al.[19] was rated at moderate risk due to smaller sample size, though it offered valuable insights into the feasibility of self-sampling. Collectively, the risk of bias across the included studies was judged to be low to moderate, suggesting that the findings of this meta-analysis are reliable and unlikely to be significantly undermined by methodological weaknesses.

DISCUSSION

This meta-analysis provides a summary evaluation of the Genoflow HPV Array test in ten studies between 2010 and 2025, pooling evidence from different geographic settings and methodological contexts. The investigations, conducted in Asia, Europe, South America, and the Middle East, tested Genoflow either as a sole primary genotyping reagent or in comparison to established assays such as PCR-based assays, Roche Linear Array, Reverse Line Blot, Onclarity, and next-generation sequencing (NGS). The broad scope of study populations and diagnostic contexts highlights not just the universal utility but also the methodological flexibility of Genoflow.

Pooled prevalence analysis reaffirmed the preponderance of HPV-16 and HPV-18 as the principal oncogenic genotypes, with rising prevalence of HPV-16 from 22% in CIN1 to 65% in invasive cervical cancer, and HPV-18 from 6% to 21% along the same continuum. These results are consistent with worldwide epidemiologic evidence that incriminates these two types in the etiology of the majority of cervical cancers. Interestingly, other high-risk types, like HPV-31, 33, and 45, were also present at lower but consistent frequencies, while HPV-52 and HPV-58 were particularly notable for being exceptionally prominent in CIN2/3 and cancer. The significant roles of HPV-52 and HPV-58 are in agreement with previous regional studies in Asia, emphasizing the needs for extended vaccine formulations and region-specific screening programs taking into account genotype diversity beyond HPV-16/18.

The diagnostic concordance testing showed that Genoflow is reproducible when compared to reference assays. High concordance with Roche Linear Array (88–92%) was seen in two early validation studies, with CIN2+ sensitivity and specificity consistently 88–89% and 87%, respectively. Reverse Line Blot was found to have an equivalent agreement of 90%, with discrepancies for uncommon genotypes. Onclarity comparison yielded modestly lower concordance (~88%), with misclassification noted in longer genotyping contexts. In comparison, PCR-based assays and NGS had higher concordance, 89–95%, with NGS having higher sensitivity (92–94%) and specificity (93–95%). These findings reinforce Genoflow as a robust genotyping method in clinical and epidemiological practice but also highlight its limitations relative to sequencing-based platforms, particularly for low-abundance or phylogenetically similar genotypes.

Study-level comparison also works to bring out the strengths and weaknesses of Genoflow. The first validation studies determined its concordance with Linear Array while also highlighting its ability to detect a greater number of multiple infections.[21,22] Subsequent studies took its application even further: Rohner et al.[26] and Indarti et al.[19] determined its reliability in the context of self-sampling, advancing its potential for expanding screening in low-resource settings. Alhamlan et al.[27] highlighted its reliability in detecting common oncogenic genotypes but also its limitations in rarer variants. More recent comparisons with NGS consistently confirmed its strong overall concordance, while simultaneously underscoring the superior resolution of NGS in identifying low-copy-number infections.[23,25] Epidemiological applications, such as Chakraborty et al.[18], further validated its practical value for mapping genotype distributions in low-resource settings, despite the absence of comparator assays.

Risk of bias assessment indicates that the quality of included studies was overall acceptable, with most studies being rated as low risk. Early validation and multi-platform comparisons more recently demonstrated superb methodological rigor. Moderate risk was apparent in small-scale studies or single-method design studies lacking comparators, but these did not significantly subtract from the pooled findings.[18-20] Misclassification issues reported in Wong et al.[24] offer an important warning on Genoflow's capacity to differentiate between near-neighbor genotypes, i.e., HPV-33 and HPV-35, and the need for confirmatory approaches in studies where precise genotype resolution is critical.

Together, these findings position Genoflow as an affordable, sensitive, and versatile HPV genotyping reagent that stands up to PCR-based methods and can feasibly be deployed in both lab and field environments. Its strong points include being able to identify multiple infections, being suitable for self-sampling, and being relatively inexpensive when compared with sequencing technologies. However, its lack of discrimination between phylogenetically closely related types and its lower sensitivity than NGS highlight the necessity for careful interpretation and, where feasible, complementary confirmation. Multicenter research on a large scale comparing Genoflow and NGS directly, particularly in settings with a high burden, must be a priority to clarify the extent of genotype-specific detection differences. These activities will be central to ensuring that HPV genotyping platforms provide data that are of high quality for screening policy-informed, vaccination policy-informed, and, ultimately, global cervical cancer elimination activity contributions.

CONCLUSION

This meta-analysis demonstrates the Genoflow HPV Array to be a cost-effective, precise genotyping platform with high concordance to reference PCR-based assays and with excellent relevance to different clinical and epidemiological situations. HPV-16 and HPV-18 remain the most common oncogenic types at every stage of disease, while HPV-52 and HPV-58 contribute to higher-grade lesions, particularly in Asian populations. Though Genoflow performs adequately, occasional misclassification and lower sensitivity compared to NGS reflect its shortcomings. Despite this, its inexpensiveness, ability to multiplex detect, and practicability to self-sampling make it a treasure in low-resource settings, enabling evidence-based screening, vaccination, and elimination of cervical cancer strategies.

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