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Predictive risk assessment and targeted testing could enhance STI diagnosis in a high HIV prevalence setting in Eswatini

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Sexually transmitted infections (STIs) present significant public health challenges in resource-limited settings where syndromic management, which often leads to misdiagnosis and over-treatment, remains standard care. We retrospectively evaluated hypothetical STI risk assessment-only (Triage-only) and sequential risk assessment plus STI diagnostic testing (Triage&Test) approaches as potential enhancements to syndromic management in a high-burden setting. A retrospective analysis was conducted using historic data from a cross-sectional study of adults (≥ 18 years) accessing six outpatient care sites in Eswatini between July 2022 and April 2023. Clinical records included STI risk factor assessments, outcomes of syndromic assessment for vaginal discharge syndrome (VDS) and male urethritis syndrome (MUS), leukocyte esterase (LE) and HIV testing, and molecular-based testing for Chlamydia trachomatis (CT), Neisseria gonorrhoeae (NG), and Trichomonas vaginalis (TV). Sex-specific predictive risk scores (PRS) tools for CT/NG/TV infections were developed using LASSO penalized logistic regression. Subsequently, the diagnostic performance of various hypothetical Triage-only and Triage&Test approaches was compared to molecular-based testing for CT/NG/TV infections. The aim was to identify strategies meeting programmatic benchmarks of ≥ 90% sensitivity and < 60% testing efficiency. Of 1396 participant records analysed, 65.4% (n = 913) were women and the median age was 29 years (IQR 23–36). Triage-only approaches underperformed, resulting in high proportions of false-positive and false-negative cases. Specifically, VDS showed a sensitivity of only 32.9% (95% CI 27.5–38.6) and a specificity of 75.1% (95% CI 71.5–78.5), while MUS had a sensitivity of 65.0% (95% CI 57.0–72.4) and specificity of 88.0% (95% CI 84.0–91.4). All PRS tools configurations in simulated Triage&Test approaches outperformed Triage-only methods by reducing false-negative and eliminating false-positive cases, thus achieving 100% specificity and positive-predictive value. Despite these improvements, no Triage&Test approach fully met established benchmarks. The highest sensitivity, observed in men, was 91.1% (95% CI 85.5–95) with an efficiency of 86.0%. In women, the best sensitivity was 79.0% (95% CI 73.8–83.6) at an efficiency of 60.1%. While PRS tools integrated within Triage&Test approaches may improve STI diagnosis in high-burden settings, challenges in balancing accuracy and resource demands persist. Access to affordable and well-targeted point-of-care rapid diagnostic tests appears essential to improve STI care quality in resource-limited environments.

Keywords Sexually transmitted infections, HIV, Syndromic management, Predictive risk score, Coinfections, Triage

Sexually transmitted infections (STIs) are a global public health concern, causing significant morbidity and healthcare costs[1]. Common curable bacterial and protozoan STIs include Chlamydia trachomatis (CT), Neisseria gonorrhoeae (NG), and Trichomonas vaginalis (TV), with more than 1 million new infections estimated

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globally each day[1]. These infections can cause adverse outcomes, including pelvic inflammatory disease, ectopic pregnancy, infertility, and increased HIV risk[2–4]. Asymptomatic STIs, especially in women, complicate diagnosis, increasing the risk of ongoing transmission and adverse health outcomes[5].

Current approaches for diagnosing STIs in resource-limited settings typically rely on syndromic assessment and management. It often results in misdiagnosis and overtreatment due to its reliance on clinical symptoms that are unspecific to particular pathogens[6]. Molecular-based laboratory tests for diagnosing CT, NG and TV are increasingly used in well-resourced settings, as targeted pathogen detection and tailored treatments are crucial, particularly due to rising global concern of antimicrobial resistance in NG[1,7]. While these tests offer higher sensitivity, specificity, and the ability to detect a broad range of pathogens, this capability demands significant infrastructure and resources, often making them infeasible in resource-limited settings[1,7–10].

Therefore, there is an urgent need to improve and adapt the management of these infections to the current context. Predictive risk scoring has emerged as a potential tool to identify individuals at high risk of bacterial and viral STIs as well as sexual risk behaviours[11–15]. These predictive risk score (PRS) tools integrate demographic, behavioural, and clinical factors to stratify individuals according to their risk of having an STI. This approach aims to streamline the allocation of diagnostic resources, improving the cost-effectiveness of case-finding programs and reducing the incidence of these infections through targeted interventions[6,11,12,14]. Although promising, these tools require rigorous development and validation across diverse populations and settings to ensure their accuracy and reliability in predicting STIs.

In Eswatini, the burden of curable STIs is high, with a combined prevalence of 25.0% for CT, NG and TV among young women[16,17], alongside an adult HIV prevalence of 24.8%[18]. Syndromic management has remained the standard approach to STI care, as access to molecular-based testing was limited. In this context, we evaluated whether a predictive, symptom- and risk-based triage tool based on symptoms and reported risk behaviours could improve the efficiency of molecular-based STI testing by developing and assessing the performance of sex-specific PRS tools to prioritise clients for testing and thereby enhance case detection.

Methods

Setting

Shiselweni in southern Eswatini had ~ 203,000 residents and 26·5% HIV prevalence in 2021[18,19]. STIs care was integrated into routine outpatient and HIV services at primary and secondary care levels. While HIV testing was routinely conducted using rapid diagnostic tests, molecular-based testing for CT, NG, and TV was rarely available in outpatient care. GeneXpert platforms were primarily located at referral or sentinel sites and were mainly used for tuberculosis diagnosis and, to some extent, HIV viral load testing. STI diagnosis relied on syndromic management and universal molecular-based testing for CT, NG and TV was deemed infeasible due to limited financial resources.

Study design

We conducted a retrospective analysis based on historic data from a cross-sectional study of adults (≥ 18 years) who received STI risk assessment and testing services at six outpatient care sites in Shiselweni, Eswatini, between July 2022 and April 2023. In the original study, participants had undergone syndromic assessment and evaluation for STI risk factors, and received a range of diagnostic tests, including molecular-based testing for CT, NG, and TV. The main objective of this retrospective analysis was to evaluate the performance of hypothetical PRS tools and alternative risk assessment approaches to guide potential future use of targeted molecular STI testing.

Procedures

The original larger study that assessed the burden of STIs in this setting has been described elsewhere[20,21]. In summary, clients accessed four public sector care sites under the Ministry of Health and two community-based sites operated by Médecins Sans Frontières. Main entry points included HIV testing services, antiretroviral therapy (ART) refills, and referrals from general outpatient care for clients suspected of having STIs. Following informed written consent, participants completed a self-questionnaire in electronic or paper formats. In addition to routine care that included rapid-diagnostic HIV testing, nurses employed the syndromic approach to evaluate all clients for signs and symptoms of STIs. Patient self-collected urine samples were tested on-site for leukocyte esterase (LE) reactivity and pregnancy. Thereafter, urine samples were sent to Nhlangano laboratory for molecular-based testing conducted by laboratory technicians using the Xpert platform to detect CT, NG, and TV pathogens. Plasma samples were used to test for acute HIV infection using viral load quantification on Xpert. No rapid test was performed for genital ulcers, but plasma samples from all participants were sent to a laboratory in South Africa for serologic HSV-2 testing. Individuals with vaginal discharge syndrome (VDS) or male urethritis syndrome (MUS) received prompt standardized therapy, with adjustments guided by Xpert results as necessary.

Evaluation of risk assessment and testing approaches

We evaluated the diagnostic performance of several hypothetical STI risk assessment and testing strategies in a stepwise manner as illustrated in Fig. 1 (Panels A–C). Molecular-based testing served as the gold standard for infection status. In this analysis, the term 'triage' refers to the use of syndromic assessment—either alone or in combination with other factors such as LE testing—and/or predictive risk scoring to identify individuals at increased risk of CT/NG/TV infection for confirmatory testing in sequential approaches or for presumptive treatment.

The performance of the PRS tools was assessed in two ways: first, as a stand-alone diagnostic decision-making tool within Triage-only scenarios – thus serving a similar function to, and potentially replacing, the existing

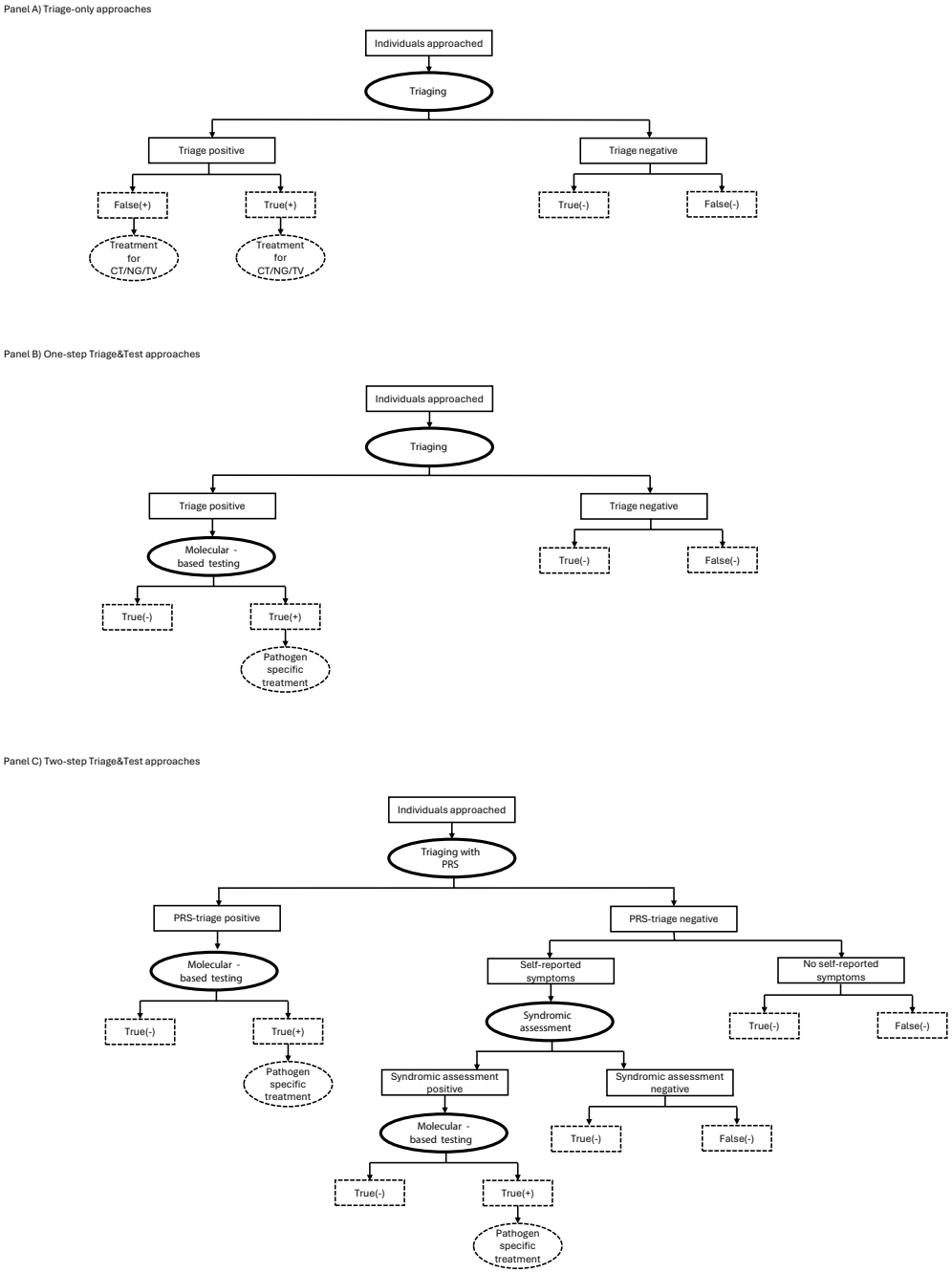

Fig. 1. Flow charts of Triage-only (Panel **A**), one-step Triage&Test (Panel **B**) and two-step Triage&Test approaches (Panel **C**). Triage-only approaches refer to strategies where clients identified as positive are presumptively treated without confirmatory testing. The following four approaches were assessed: (1) Syndromic assessment alone (vaginal discharge syndrome [VDS] for women, male urethritis syndrome [MUS] for men), (2) Syndromic assessment and/or a positive leukocyte esterase (LE) result, (3) Sex-specific predictive risk score (PRS) tools, with one developed for women and two distinct tools for men. *PRS* predictive risk score, *PRS-w* predictive risk score tool for women with a cut-off ≥ 1, *PRS-m1* predictive risk score tool 1 for men with a cut-off ≥ 18, *PRS-m2* predictive risk score tool 2 for men with a cut-off ≥ 25.

syndromic assessment and management approach; and second, as an STI risk stratification tool to identify and guide clients for targeted molecular testing under the Triage&Test approaches.

Triage-only approaches (Fig. 1, Panel A)

First, we retrospectively assessed the performance of four hypothetical risk assessment approaches that reflect current or plausible programmatic practices, in which individuals identified as positive (e.g., syndromic approach) or meeting higher risk criteria (e.g., PRS) are treated presumptively. These methods included: (1)

syndromic assessment (VDS in women, MUS in men) based on current WHO guidelines; (2) a combined indicator of syndromic assessment and/or a positive LE result; (3) self-reported STIs-like symptoms only; and (4) newly developed sex-specific PRS tools for the detection of CT/NG/TV infection.

One-step triage and test strategies (Fig. 1, Panel B)
We then simulated a one-step Triage&Test scenario, in which the same four risk assessment approaches described above were applied, followed by confirmatory molecular-based testing using GeneXpert for individuals meeting the triage criteria. This sequential and targeted diagnostic strategy aimed to improve diagnostic accuracy and reduce overtreatment.

Two-step triage and test strategy (Fig. 1, Panel C)
Finally, we assessed a two-arm, sequential two-step Triage&Test approach. This approach combined (1) PRS-based risk assessment tools (arm 1) and (2) self-reported symptom-based assessment followed by syndromic criteria among individuals not meeting the PRS triage criteria (arm 2). Only individuals meeting the triage criteria in both arms proceeded to confirmatory molecular-based testing. The approach aimed to improve specificity while maintaining high sensitivity.

Main definitions

VDS and MUS were diagnosed by clinicians following the syndromic approach outlined in the national treatment guidelines[22]. It identified a clinical syndrome and recommended standardized treatments for the most likely pathogens associated with the syndrome. CT/NG/TV infection was defined as the presence of one or more of these pathogens (Chlamydia trachomatis, Neisseria gonorrhoeae, or Trichomonas vaginalis) based on molecular-based test results, irrespective of whether patients presented with symptoms suggestive of infection. A new diagnosis of established HIV infection was defined as a client with reactive results on both the Alere Determine™ and Uni-Gold™ rapid diagnostic tests, performed using a serial HIV testing algorithm. Acute/early HIV infection was a case with either (1) a negative Alere Determine™ result with an elevated HIV viral load, or (2) discordant results (Determine™ positive and Uni-Gold™ negative) with an elevated HIV viral load. STI symptoms referred to patient self-reported experiences of any of the following: genital discharge, genital itchiness, pain when urinating, pain during sex, lower abdominal pain (in women), or scrotal swelling (in men).

Testing efficiency was defined at a cutoff point < 60%, aiming at any Triage&Test approach to direct < 60% of assessed clients toward confirmatory laboratory testing. This benchmark, as proposed in similar STIs studies[11,23–25], aims to optimize resource utilization while maintaining a high degree of accuracy in identifying cases requiring further diagnostic evaluation. The benchmark for optimal sensitivity of Triage&Test approaches was defined as ≥ 90%[11].

Data management

We emulated a real-world clinical scenario in our analyses, recognising that healthcare providers often make decisions based on incomplete or inaccurate information (e.g., missing test results or uncertain responses regarding sexual risk behaviours). To reflect this, we assigned a code of one to all positive responses and test results, while combining negative, missing, or '*don't know*' responses into a single category coded as zero.

Statistics

Statistical analyses were performed with Stata 18 and stratified by sex. First, we describe baseline characteristics as counts and proportions for categorical variables and as medians with interquartile range (IQR) for continuous variables.

Development of sex-specific PRS tools
We developed sex-specific PRS tools that aimed to predict the individual´s risk of presenting with CT/NG/TV infection based on their distinctive combination of baseline characteristics. Characteristics were chosen based on existing knowledge of factors potentially associated with CT/NG/TV infection and other STIs (e.g., Treponema pallidum, acute/established HIV, HSV-2) and encompassed facility-level and socio-demographic variables, patient self-reported symptoms and behavioural determinants, clinical signs assessed by the nurse including the outcomes of syndromic assessment, as well as the test results of viral STIs (HIV, HSV-2) and other rapid diagnostic tests (urine strip for LE testing, and pregnancy) that may be associated with infection. Variables assessed for potential inclusion comprised all available factors.

The sex-specific PRS tools were developed using least absolute shrinkage and selection operator (LASSO) logistic regression with tenfold cross-validation. This approach allowed us to identify the most relevant variables by selecting non-zero coefficients from a standardized set of predictors. For each participant, a total predictive score was calculated by summing the selected coefficients, multiplying the result by 100, and rounding to the nearest integer. Sensitivity and testing efficiency were then evaluated for different cut-off points, with the goal of achieving a sensitivity ≥ 90% and efficiency < 60%, where feasible. Further technical details, including the encoding of categorical variables and model calibration procedures, are provided in Supplementary Text 1 and illustrated in Supplementary Figs. 1 and 2.

Performance of triage-only and triage and test approaches
The performance of Triage-only and two-step Triage&Test approaches were assessed by plotting receiver operating characteristic (ROC) curves and estimating the area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The PPV and NPV were determined

using a prevalence estimate of 30% for CT/NG/TV infection. Finally, real-world testing efficiency was compared between the different approaches using the benchmarks of sensitivity and efficiency.

Ethics

This study received approval from the Eswatini Health and Human Research Review Board (EHHRRB096/2021) and the MSF Ethics Review Board (ID: 2154).

Results

Baseline characteristics

Of the 1396 participants records analysed, 65·4% (n = 913) were women and the median age was 29 (IQR 23–36) years. Prior to routine HIV testing, 19·6% (274) of clients were known HIV-positive, more among women (24·2%) than men (11·0%, $p < 0·001$).

In summary, most clients (90·4%) reported being in a relationship, with over half (52·8%) perceiving themselves at risk of STI infection, and 30·9% having had two or more sexual partners in the past six months. Approximately 15·7% of clients indicated that their sexual partner had an STI during the same period. Reported behavioural risk factors included the use of alcohol before sex (19·3%), engagement in anal sex (4·1%), and participation in transactional sex. Overall, 17·1% had strong LE reactivity, 3·3% were newly diagnosed with HIV, and 56·7% showed signs of previous or chronic HSV-2 infection, while 9·7% had evidence of active or treated syphilis infection. The most prevalent self-reported symptoms suggestive of STIs were genital discharge (34·2%) and genital itchiness (35·9%). Following syndromic assessment, the most likely diagnoses were MUS in men (29·2%), and VDS in women (27·4%), with genital ulcer syndrome (GUS) affecting 5·9% of the entire study population. A wide range of baseline factors differed between the sexes, as presented in Table 1.

According to the molecular-based test results, 443 (31·7%) clients had CT/NG/TV infection. The prevalence was 31·3% (286/913) in women and 32·5% (157/326) in men.

Sex-specific PRS tools

Details on model calibration and the final selection of non-zero coefficients for the refined sex-specific PRS tools are presented in Supplementary Text 1 and Supplementary Tables 1 and 2. Sex-specific sensitivity, specificity, and efficiency estimates for various predictive cut-off levels are presented in Fig. 2. Following the prior established benchmarks, in women, no cut-off threshold reached 90% sensitivity. A predictive score cut-off of ≥ 1 achieved a sensitivity of 79·0% (95% CI 73·8–83·6) with an efficiency of 60·1% (PRS-women). In men, two predictive cut-off thresholds were identified. A predictive score cut-off of ≥ 18 achieved a sensitivity of 91·1% (95% CI 85·5–95·0) with an efficiency of 66·0% (PRS-men-1). A cut-off of ≥ 25 achieved an efficiency of 60·0% with a sensitivity of 86·6% (95% CI 80·3–91·5) (PRS-men-2).

These identified cut-off levels were used for the sex-specific PRS tools (1 for women, 2 for men), whose diagnostic performance was further evaluated in the Triage-only and Triage&Test approaches.

Performance of triage-only and Triage&Test approaches

Triage-only approaches

The overall performance of various Triage-only approaches are presented in Fig. 3 and Table 2 (Panel A). Overall, the ROC area ranged between 0·54 and 0·64 in women for the different Triage-only approaches, and from 0·66 to 0·77 in men respectively (Fig. 3). Syndromic assessment for VDS had the lowest sensitivity at 32·9% (95% CI 27·5–38·6) at a specificity of 75·1% (95% CI 71·5–78·5). Relying on client self-reported symptoms and the PRS tools in women, both achieved sensitivities of approximately 79% and specificities around 50%. In men, syndromic assessment for MUS yielded a sensitivity of 65·0% (95% CI 57·0–72·4) and a specificity of 88·0% (95% CI 84·0–91·4). The PRS-men-1 and PRS-men-2 tools exhibited the highest sensitivities among all approaches (PRSm-1: 91·1%, 95% CI 85·5–95·0; PRSm-2: 86·6%, 95% CI 80·3–91·5), with specificities approximately at 50%. For both sexes, combining syndromic assessment with a positive LE test result increased sensitivity compared to syndromic assessment only, though specificity remained low, particularly in women (Table 2).

Figure 4 (Panel A) illustrates the true and false classifications of test results. Generally, the proportion of false-positive cases is high, and moderate for false-negative cases, with Triage-only approaches performing worse in women than in men.

One-step triage and test approaches

With one-step Triage&Test approaches (Table 2, Panel B), sensitivity remains the same as for Triage-only approaches. However, inclusion of testing eliminates false-positive cases as shown (Fig. 4, Panel B), allowing all approaches to achieve a specificity and PPV of 100% (Table 2, Panel B). Considering the sensitivity and efficiency benchmarks, all PRS tools configurations performed better, with fewer false-negative cases than syndromic assessment, combined syndromic assessment with LE testing, and patient self-reported symptom-based assessment.

Two-step triage and test approaches

For both sexes, all two-step approaches continued not to have false-positive cases (Fig. 4, Panel C). In women, eight additional cases of infection were identified, increasing sensitivity from 79·0% in the one-step approach to 81·8%, and the NPV from 91·8 to 92·8% (Table 2, Panel C). Approximately one quarter (26·5%) of women would need to undergo syndromic assessment (as they were PRS tool negative but presented with symptoms suggestive of STIs), and efficiency increased from 60·1 to 66·4%. In men (Table 2, Panel C), the two-step Triage&Test approach did not identify any additional cases of infection, thus the testing performance indicators remained

	Baseline characteristics						
	Total		Females		Males		
	N	%	N	%	N	%	p-value[1]
Total number (denominator)	1396		913		483		
Clinic factors							
Known HIV + (at clinic visit)	274	(19.6)	221	(24.2)	53	(11.0)	< 0.001
Entry point: Referral from OPD	318	(22.8)	211	(23.1)	107	(22.2)	0.685
Entry point: HIV treatment	185	(13.3)	144	(15.8)	41	(8.5)	< 0.001
Entry point: HIV testing	892	(63.9)	558	(61.1)	334	(69.2)	0.003
Visit reason: Feeling sick	439	(31.4)	271	(29.7)	168	(34.8)	0.051
Visit reason: Maternal care	87	(6.2)	77	(8.4)	10	(2.1)	< 0.001
Visit reason: Tuberculosis	9	(0.6)	5	(0.5)	4	(0.8)	0.533
Visit reason: HIV prevention	123	(8.8)	67	(7.3)	56	(11.6)	0.008
Visit reason: Family planning	157	(11.2)	121	(13.3)	36	(7.5)	0.001
Visit reason: STI care	64	(4.6)	58	(6.4)	6	(1.2)	< 0.001
Visit reason: Partner notification	36	(2.6)	15	(1.6)	21	(4.3)	0.002
Socio-demographic factors							
Age: 18–29	754	(54.0)	505	(55.3)	249	(51.6)	0.180
Age: 30–39	409	(29.3)	261	(28.6)	148	(30.6)	0.422
Age: 40–49	176	(12.6)	113	(12.4)	63	(13.0)	0.721
Age: ≥ 50	57	(4.1)	34	(3.7)	23	(4.8)	0.351
Education: None	33	(2.4)	17	(1.9)	16	(3.3)	0.090
Education: Primary school	164	(11.7)	109	(11.9)	55	(11.4)	0.761
Education: Secondary school	341	(24.4)	237	(26.0)	104	(21.5)	0.067
Education: High school	634	(45.4)	411	(45.0)	223	(46.2)	0.681
Education: Tertiary education	216	(15.5)	133	(14.6)	83	(17.2)	0.198
Employed	537	(38.5)	293	(32.1)	244	(50.5)	< 0.001
Self-employed	144	(10.3)	81	(8.9)	63	(13.0)	0.015
Part-time worker	85	(6.1)	52	(5.7)	33	(6.8)	0.398
Unemployed	623	(44.6)	482	(52.8)	141	(29.2)	< 0.001
Factory worker	195	(14.0)	126	(13.8)	69	(14.3)	0.804
Reproductive factors							
Thinking to have a child	366	(26.2)	233	(25.5)	133	(27.5)	0.415
Known pregnancy	160	(11.5)	160	(17.5)	0	(0.0)	< 0.001
Lactating	94	(6.7)	94	(10.3)	0	(0.0)	< 0.001
Behavioural factors							
Married	305	(21.8)	220	(24.1)	85	(17.6)	0.005
In a relationship	1262	(90.4)	827	(90.6)	435	(90.1)	0.754
Feeling at risk of HIV (since last sex)	517	(37.0)	308	(33.7)	209	(43.3)	< 0.001
Feeling at risk of HIV (past 6 mo)	465	(33.3)	275	(30.1)	190	(39.3)	0.001
Feeling at risk of STI (past 6 mo)	737	(52.8)	444	(48.6)	293	(60.7)	< 0.001
Alcohol use prior sex (past 6 mo)	270	(19.3)	109	(11.9)	161	(33.3)	< 0.001
Used (injectable) drugs	21	(1.5)	13	(1.4)	8	(1.7)	0.734
Exchange goods for sex	60	(4.3)	36	(3.9)	24	(5.0)	0.369
Receive goods for sex	73	(5.2)	53	(5.8)	20	(4.1)	0.184
Did not use condom (past 6 mo)	988	(70.8)	650	(71.2)	338	(70.0)	0.635
Did not use condom (since last HIV test)	554	(39.7)	338	(37.0)	216	(44.7)	0.005
Anal sex (past 6 mo)	57	(4.1)	31	(3.4)	26	(5.4)	0.074
Exposed to body fluids (past 6 mo)	710	(50.9)	452	(49.5)	258	(53.4)	0.165
Number of sex partners (past 6 mo): 1	905	(64.8)	689	(75.5)	216	(44.7)	< 0.001
Number of sex partners (past 6 mo): 2	321	(23.0)	156	(17.1)	165	(34.2)	< 0.001
Number of sex partners (past 6 mo): ≥ 3	110	(7.9)	27	(3.0)	83	(17.2)	< 0.001
Non sex partner (past 6 mo)	58	(4.2)	41	(4.5)	17	(3.5)	0.387
More than 1 sex partner (since last HIV test)	402	(28.8)	191	(20.9)	211	(43.7)	< 0.001
Age difference: 0–5 years	972	(69.6)	616	(67.5)	356	(73.7)	0.016
Age difference: 6–10 years	333	(23.9)	233	(25.5)	100	(20.7)	0.045
Age difference: 11–15 years	58	(4.2)	42	(4.6)	16	(3.3)	0.251
Continued							

	Baseline characteristics						
	Total		Females		Males		
	N	%	N	%	N	%	p-value[1]
Age difference: ≥ 16 years	33	(2.4)	22	(2.4)	11	(2.3)	0.877
Treated for STI (past 6 mo)	369	(26.4)	220	(24.1)	149	(30.8)	0.006
Treated for STI (since last HIV test)	285	(20.4)	163	(17.9)	122	(25.3)	0.001
Sex partner had STI (past 6 mo)	219	(15.7)	123	(13.5)	96	(19.9)	0.002
≥ 1 sex partner known HIV +	244	(17.5)	154	(16.9)	90	(18.6)	0.409
≥ 1 sex partner unknown HIV status	642	(46.0)	382	(41.8)	260	(53.8)	< 0.001
Last sex: < 24 h	102	(7.3)	61	(6.7)	41	(8.5)	0.217
Last sex: 1 week	470	(33.7)	273	(29.9)	197	(40.8)	< 0.001
Last sex: 2 weeks	263	(18.8)	176	(19.3)	87	(18.0)	0.565
Last sex: 3–4 weeks	226	(16.2)	159	(17.4)	67	(13.9)	0.087
Last sex: > 1 to 6 month	271	(19.4)	202	(22.1)	69	(14.3)	< 0.001
No sexual encounter past 6 months	58	(4.2)	39	(4.3)	19	(3.9)	0.763
HIV care factors							
Last HIV test: 1 months	304	(21.8)	197	(21.6)	107	(22.2)	0.804
Last HIV test: 2–3 months	323	(23.1)	213	(23.3)	110	(22.8)	0.815
Last HIV test: 4–6 months	219	(15.7)	149	(16.3)	70	(14.5)	0.372
Last HIV test: ≥ 6 months	474	(34.0)	317	(34.7)	157	(32.5)	0.406
Never tested for HIV	58	(4.2)	26	(2.8)	32	(6.6)	0.001
Using ART	270	(19.3)	218	(23.9)	52	(10.8)	< 0.001
Used/ using PREP (past 6 mo)	124	(8.9)	86	(9.4)	38	(7.9)	0.332
Considering PREP in future	490	(35.1)	288	(31.5)	202	(41.8)	< 0.001
Self-reported symptoms							
Red eyes	346	(24.8)	234	(25.6)	112	(23.2)	0.315
Headache	628	(45.0)	457	(50.1)	171	(35.4)	< 0.001
Fever	282	(20.2)	189	(20.7)	93	(19.3)	0.522
Fatigue	554	(39.7)	387	(42.4)	167	(34.6)	0.005
Body pain	453	(32.4)	312	(34.2)	141	(29.2)	0.059
Weight loss	274	(19.6)	168	(18.4)	106	(21.9)	0.113
Night sweat	187	(13.4)	93	(10.2)	94	(19.5)	< 0.001
Cough	282	(20.2)	185	(20.3)	97	(20.1)	0.936
Sore throat	207	(14.8)	146	(16.0)	61	(12.6)	0.093
Diarrhoea	126	(9.0)	85	(9.3)	41	(8.5)	0.610
White faeces	35	(2.5)	29	(3.2)	6	(1.2)	0.028
Dark urine	67	(4.8)	37	(4.1)	30	(6.2)	0.073
Red urine	117	(8.4)	62	(6.8)	55	(11.4)	0.003
Nausea	241	(17.3)	189	(20.7)	52	(10.8)	< 0.001
Vomiting	117	(8.4)	99	(10.8)	18	(3.7)	< 0.001
Abdominal pain	565	(40.5)	481	(52.7)	84	(17.4)	< 0.001
Body rash	198	(14.2)	125	(13.7)	73	(15.1)	0.469
Swollen glands	77	(5.5)	45	(4.9)	32	(6.6)	0.187
Mouth sores	76	(5.4)	42	(4.6)	34	(7.0)	0.056
Scrotal swelling	22	(1.6)	0	(0.0)	22	(4.6)	< 0.001
Genital itchiness	501	(35.9)	320	(35.0)	181	(37.5)	0.369
Genital warts	131	(9.4)	81	(8.9)	50	(10.4)	0.367
Genital sores	193	(13.8)	112	(12.3)	81	(16.8)	0.020
Genital discharge	477	(34.2)	341	(37.3)	136	(28.2)	0.001
Pain when urinating	364	(26.1)	199	(21.8)	165	(34.2)	< 0.001
Pain during intercourse	329	(23.6)	260	(28.5)	69	(14.3)	< 0.001
Clinical signs							
Body rash	89	(6.4)	56	(6.1)	33	(6.8)	0.611
Pharyngitis	36	(2.6)	24	(2.6)	12	(2.5)	0.872
Jaundice	3	(0.2)	1	(0.1)	2	(0.4)	0.242
Conjunctivitis	26	(1.9)	16	(1.8)	10	(2.1)	0.676
Oral blisters/ sores	23	(1.6)	13	(1.4)	10	(2.1)	0.367
Continued							

	Baseline characteristics						
	Total		Females		Males		
	N	%	N	%	N	%	p-value[1]
Abdominal tenderness	84	(6.0)	72	(7.9)	12	(2.5)	< 0.001
Swollen extrainguinal lymphnodes	5	(0.4)	2	(0.2)	3	(0.6)	0.232
Genial ulcer	71	(5.1)	36	(3.9)	35	(7.2)	0.008
Genital blisters	36	(2.6)	17	(1.9)	19	(3.9)	0.020
Genital warts	53	(3.8)	34	(3.7)	19	(3.9)	0.845
Scrotal swelling	5	(0.4)	0	(0.0)	5	(1.0)	0.002
Vaginal inflammation	94	(6.7)	94	(10.3)	0	(0.0)	< 0.001
Vaginal bleeding	31	(2.2)	31	(3.4)	0	(0.0)	< 0.001
Test results							
LE: Negative	804	(57.6)	502	(55.0)	302	(62.5)	0.007
LE: Trace	86	(6.2)	61	(6.7)	25	(5.2)	0.266
LE: Weak	88	(6.3)	62	(6.8)	26	(5.4)	0.303
LE: Moderate	76	(5.4)	61	(6.7)	15	(3.1)	0.005
LE: Strong	239	(17.1)	182	(19.9)	57	(11.8)	< 0.001
Pregnancy test positive	110	(7.9)	110	(12.0)	0	(0.0)	< 0.001
Established HIV infection	36	(2.6)	27	(3.0)	9	(1.9)	0.220
Acute/early HIV infection	10	(0.7)	9	(1.0)	1	(0.2)	0.101
CT/NG/TV	443	(31.7)	286	(31.3)	157	(32.5)	0.652
TP positive	135	(9.7)	97	(10.6)	38	(7.9)	0.097
HBV positive	55	(3.9)	22	(2.4)	33	(6.8)	< 0.001
HSV-2 positive	792	(56.7)	584	(64.0)	208	(43.1)	< 0.001
Syndromic assessment outcomes							
Genital ulcer syndrome	82	(5.9)	35	(3.8)	47	(9.7)	< 0.001
Male urethritis syndrome	141	(10.1)	0	(0.0)	141	(29.2)	< 0.001
Vaginal discharge syndrome	250	(17.9)	250	(27.4)	0	(0.0)	< 0.001
Lower abdominal syndrome	169	(12.1)	169	(18.5)	0	(0.0)	< 0.001
Scrotal swelling syndrome	6	(0.4)		(0.0)	6	(1.2)	0.001
Inguinal bubo	22	(1.6)	8	(0.9)	14	(2.9)	0.004
Urinary tract infection	70	(5.0)	38	(4.2)	32	(6.6)	0.045

Table 1. Distribution of baseline characteristics overall and by sex. *ART* antiretroviral therapy, *CT/NG/TV* Chlamydia trachomatis, Neisseria gonorrhoeae, or Trichomonas vaginalis infection (one or more pathogens detected), *HBV* hepatitis B virus, *HSV-2* herpes simplex virus type 2, *mon* months, *N* number, *OPD* outpatient department, *mo* month(s), *PREP* pre-exposure prophylaxis, *p-value* differences in baseline characteristics between sexes assessed using chi-square test statistics, *STI* sexually transmitted infection(s), *TP* Treponema pallidum.

the same. A total of 11·4% (PRS-men-1) and 13·5% (PRS-men-2) of all men would need to undergo syndromic assessment, with testing efficiency slightly increased by 0·5 percentage points for both PRS tools.

Discussion

In high-income settings, universal molecular-based STI testing is increasingly feasible and highly effective for accurate case detection of CT, NG and TV. However, in Eswatini and similar low-resource contexts, routine access to molecular-based diagnostics remains limited due to test availability, infrastructure constraints, and competing priorities such as tuberculosis and HIV viral load testing. In this context, we evaluated a hypothetical, pragmatic risk-based triage approach to help prioritise clients for molecular-based STI testing. This strategy aims to enhance diagnostic yield while minimising missed infections and may serve as an interim or complementary approach where universal aetiological testing is not yet scalable. Our findings showed that Triage-only approaches yielded suboptimal results, with a high proportion of false-positive diagnoses. By integrating PRS tools into hypothetical one-step Triage&Test strategies, we improved the identification of individuals at high risk for STIs, eliminated false positives, and supported better resource allocation, particularly among men.

Interpretation of findings

Syndromic assessment, widely used in resource-poor settings, performed poorly, especially for women, consistent with two decades of similar findings[2,26,27]. Combining it with LE testing slightly improved sensitivity but remained suboptimal[14,17]. Although PRS-based triage tools are innovative and may offer a promising way forward for optimization of testing in resource-poor settings, the proportion of false-positive and false-negative

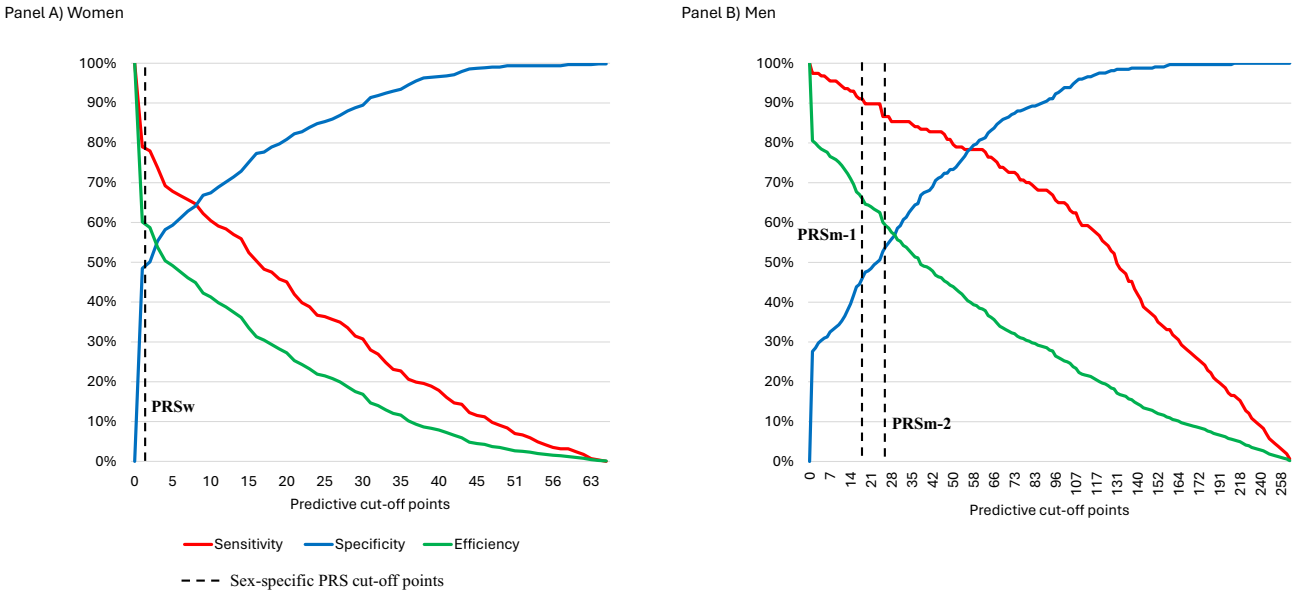

Fig. 2. Estimates of sensitivity, specificity and efficiency for the sex-specific predictive cut-off point, as well as the identified cut-off points for the predictive risk scores (PRS) tools. *LE* leukocyte esterase, *MUS* male urethritis syndrome, *PRS* predictive risk score, *ROC* receiver operating characteristic, *VDS* vaginal discharge syndrome.

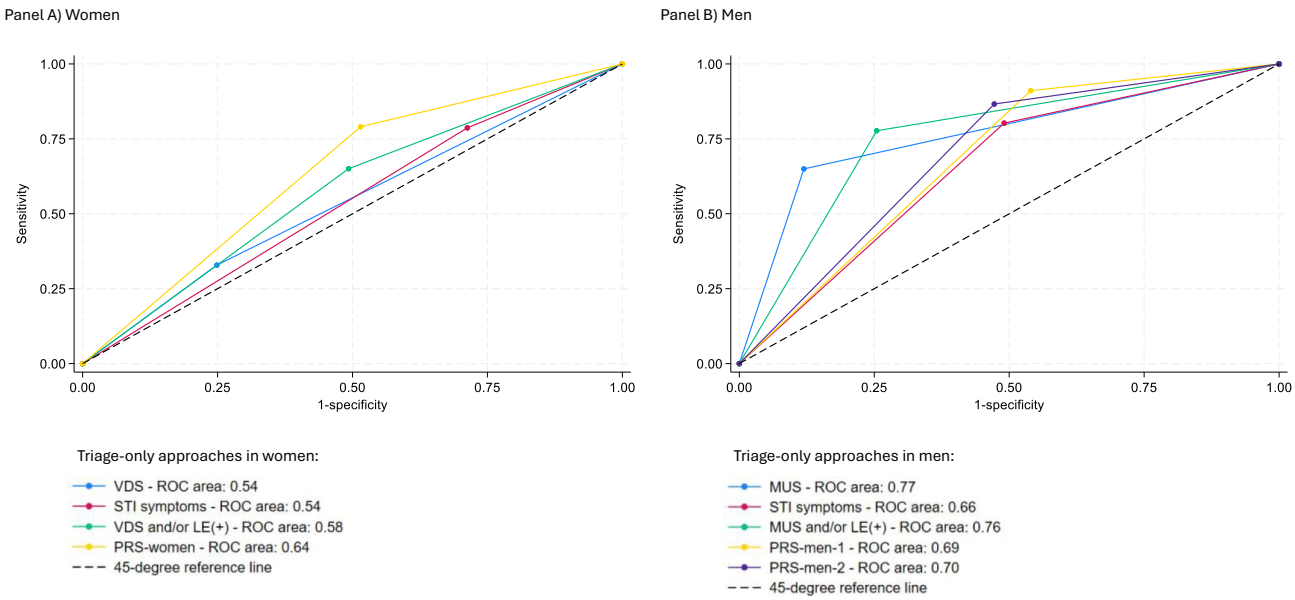

Fig. 3. Receiver operating characteristic (ROC) curves and ROC areas for Triage-only approaches in women (Panel **A**) and men (Panel **B**). *LE(+)* leukocyte esterase positive, *MUS* male urethritis syndrome, *PRS-w* predictive risk score tool for women, *PRSm-1/ PRSm-2* predictive risk scores tools 1 and 2 for men, *ROC* receiver operating characteristic, *VDS* vaginal discharge syndrome.

diagnoses remained high despite their consistently improved sensitivity. Challenges included identifying factors predicting STI risk and developing models that satisfy technical specifications. This was likely due to both the high prevalence of CT/NG/TV infections and widespread associated risk factors in this population, as similarly observed in Zimbabwe[11], making it difficult to pinpoint unique factors strongly associated with these infections. The inadequate diagnostic capability of the Triage-only approach may have resulted in the overprescription of antibiotics in false-positive cases, and likely caused unrecognized morbidity in false-negative cases, contributing to onward spread of infections. Furthermore, Triage-only approaches that omit clinical assessment for symptomatic individuals who do not meet the initial triage criteria may be unethically, thus necessitating additional confirmatory interventions such as laboratory testing or clinical assessments.

	Women				Men				
	VDS	STI symptoms	VDS and/or LE(+)	PRSw	MUS	STI symptoms	MUS and/or LE(+)	PRSm-1	PRSm-2
Panel A									
Total number	913	913	913	913	483	483	483	483	483
True negative	471 (51.6)	180 (19.7)	318 (34.8)	304 (33.3)	287 (59.4)	166 (34.4)	243 (50.3)	150 (31.1)	172 (35.6)
False negative	192 (21.0)	61 (6.7)	100 (11.0)	60 (6.6)	55 (11.4)	31 (6.4)	35 (7.2)	14 (2.9)	21 (4.3)
True positive	94 (10.3)	225 (24.6)	186 (20.4)	226 (24.8)	102 (21.1)	126 (26.1)	122 (25.3)	143 (29.6)	136 (28.2)
False positive	156 (17.1)	447 (49.0)	309 (33.8)	323 (35.4)	39 (8.1)	160 (33.1)	83 (17.2)	176 (36.4)	154 (31.9)
ROC area	0.54 (0.51–0.57)	0.54 (0.51–0.57)	0.58 (0.55–0.61)	0.64 (0.61–0.67)	0.77 (0.72–0.81)	0.66 (0.61–0.70)	0.76 (0.72–0.80)	0.69 (0.65–0.72)	0.70 (0.66–0.74)
Sensitivity	32.9 (27.5–38.6)	78.7 (73.5–83.3)	65.0 (59.2–70.6)	79.0 (73.8–83.6)	65.0 (57.0–72.4)	80.3 (73.2–86.2)	77.7 (70.4–84.0)	91.1 (85.5–95.0)	86.6 (80.3–91.5)
Specificity	75.1 (71.5–78.5)	28.7 (25.2–32.4)	50.7 (46.7–54.7)	48.5 (44.5–52.5)	88.0 (84.0–91.4)	50.9 (45.4–56.5)	74.5 (69.4–79.2)	46.0 (40.5–51.6)	52.8 (47.2–58.3)
PPV	36.1 (31.4–41.2)	32.1 (30.4–33.8)	36.1 (33.5–38.8)	39.7 (37.4–42.0)	69.9 (62.9–76.1)	41.2 (38.0–44.5)	56.7 (51.6–61.6)	42.0 (39.3–44.7)	44.0 (40.8–47.2)
NPV	72.3 (70.4–74.1)	75.8 (70.9–80.2)	77.2 (73.9–80.1)	84.4 (80.9–87.3)	85.4 (82.5–87.9)	85.7 (81.2–89.4)	88.6 (85.3–91.3)	92.3 (87.8–95.3)	90.2 (85.9–93.3)
	Women				Men				
	VDS	STI symptoms	VDS and/or LE(+)	PRSw	MUS	STI symptoms	MUS and/or LE(+)	PRSm-1	PRSm-2
Panel B									
Total number	913	913	913	913	483	483	483	483	483
True negative	627 (68.7)	627 (68.7)	627 (68.7)	627 (68.7)	326 (67.5)	326 (67.5)	326 (67.5)	326 (67.5)	326 (67.5)
False negative	192 (21.0)	61 (6.7)	100 (11.0)	60 (6.6)	55 (11.4)	31 (6.4)	35 (7.2)	14 (2.9)	21 (4.3)
True positive	94 (10.3)	225 (24.6)	186 (20.4)	226 (24.8)	102 (21.1)	126 (26.1)	122 (25.3)	143 (29.6)	136 (28.2)
False positive	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ROC area	0.66 (0.64–0.69)	0.89 (0.87–0.92)	0.83 (0.80–0.85)	0.9 (0.87–0.92)	0.83 (0.79–0.86)	0.9 (0.87–0.93)	0.89 (0.86–0.92)	0.96 (0.93–0.98)	0.93 (0.91–0.96)
Sensitivity	32.9 (27.5–38.6)	78.7 (73.5–83.3)	65 (59.2–70.6)	79 (73.8–83.6)	65 (57.0–72.4)	80.3 (73.2–86.2)	77.7 (70.4–84.0)	91.1 (85.5–95.0)	86.6 (80.3–91.5)
Specificity	100 (99.4–100)	100 (99.4–100)	100 (99.4–100)	100 (99.4–100)	100 (98.9–100)	100 (98.9–100)	100 (98.9–100)	100 (98.9–100)	100 (98.9–100)
PPV	100 (91.7–100)	100 (96.4–100)	100 (95.6–100)	100 (96.4–100)	100 (91.9–100)	100 (93.4–100)	100 (93.2–100)	100 (94.1–100)	100 (93.8–100)
NPV	77.7 (76.2–79.0)	91.6 (89.8–93.2)	87 (85.1–88.7)	91.8 (89.9–93.3)	86.9 (84.3–89.2)	92.2 (89.6–94.2)	91.3 (88.7–93.3)	96.3 (94.1–97.7)	94.6 (92.1–96.3)
Efficiency	27.4%	73.6%	54.2%	60.1%	29.2%	59.2%	42.4%	66.0%	60.0%
	PRSw & STI symptoms	PRSm-1 & STI symptoms	PRSm-2 & STI symptoms						
Panel C									
Total number	913	483	483						
True negative	627 (68.7)	326 (67.5)	326 (67.5)						
False negative	26 (2.8)	10 (2.1)	15 (3.1)						
True positive	260 (28.5)	147 (30.4)	142 (29.4)						
False positive	0 (0)	0 (0)	0 (0)						
ROC area	0.96 (0.94–0.97)	0.97 (0.95–0.99)	0.95 (0.93–0.98)						

Continued

	PRSw & STI symptoms	PRSm-1 & STI symptoms	PRSm-2 & STI symptoms						
Sensitivity	90.9 (87.0–94.0)	93.6 (88.6–96.9)	90.4 (84.7–94.6)						
Specificity	100 (99.4–100)	100 (98.9–100)	100 (98.9–100)						
PPV	100 (96.8–100)	100 (94.3–100)	100 (94.1–100)						
NPV	96.3 (94.7–97.4)	97.3 (95.3–98.5)	96.1 (93.8–97.5)						
Efficiency	86.6%	77.4%	73.5%						

Table 2. Performance of Triage-only (A), one-step (B), and two-step (C) Triage and test for identifying CT/NG/TV infections. *LE(+)* leukocyte esterase positive (trace, weak, moderate, or strong leukocyte esterase reaction), *MUS* male urethritis symptoms, *NPV* negative predictive value, *PPV* positive predictive value, *PRSm-1* predictive risk score 1 tool for men, *PRSm-2* predictive risk score 2 tool for men, *PRSw* predictive risk score tool for women, *ROC* receiver operating characteristic, *STI* sexually transmitted infection(s), *VDS* vaginal discharge symptom. *CT/NG/TV* Chlamydia trachomatis, Neisseria gonorrhoeae, or Trichomonas vaginalis infection (one or more pathogens detected); (+), positive; (-), negative.

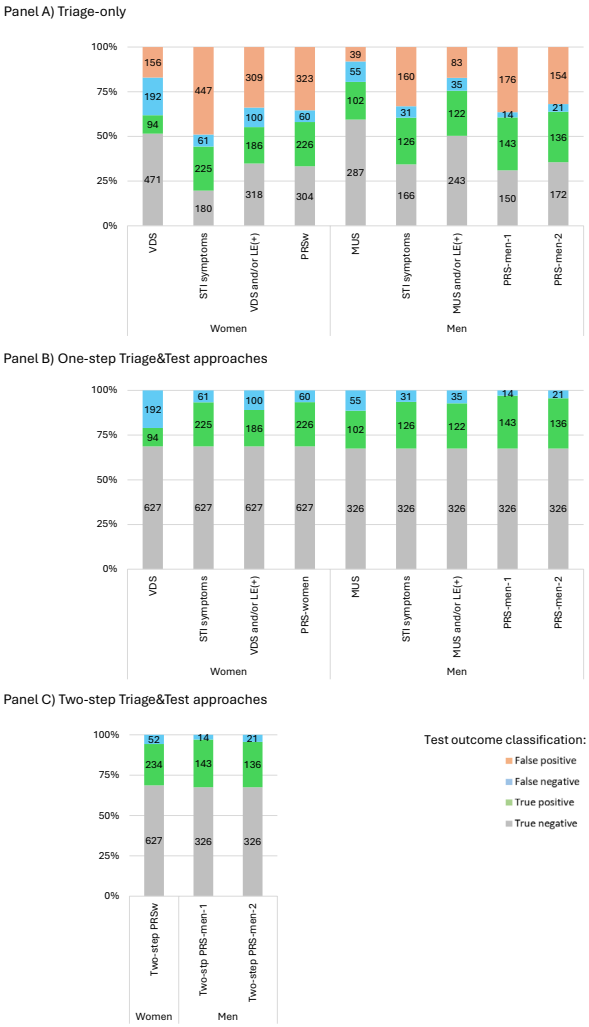

Fig. 4. Number and proportions of false/true positive and negative test results by sex for Sreen-only (Panel **A**), one-step (Panel **B**) and two-step (Panel **C**) Triage&Test approaches.

Combining triage for STI risk identification with molecular-based testing improved performance by eliminating false positives, increasing specificity and PPV to 100%, and thus supporting antibiotic stewardship through etiologic-based treatment. However, a more complex two-step Triage&Test approach did not significantly improve performance but suggested an increase in molecular-based testing and human resource requirements. The lack of added value in identifying CT/NG/TV infection in individuals who were PRS-

negative but symptomatic may indicate that any subsequent clinical assessments should possibly focus on other conditions with similar presentations, such as urinary tract infections.

Similar to other studies[14,17], LE testing improved diagnostic quality and was crucial when integrated into PRS tools. While exploring different combination of baseline factors for predicting STIs, LE test results were one of the stable variables contained in all different models, and for both men and women. While LE testing cannot differentiate specific pathogens, it remains a low-cost marker of genitourinary inflammation and, when used as part of a multivariable risk prediction tool rather than alone, may enhance targeted triage for confirmatory testing. Notably, it has been suggested since the 1990s that LE dipstick testing is effective and cost-effective for the detection of CT and NG infections and therefore should be considered routinely in STI risk assessment strategies, particularly in resource-poor settings[28].

Importantly, all Triage&Test approaches demonstrated limitations as they consistently failed to meet established programmatic benchmarks. For instance, no PRS tool cut-off level achieved 90% sensitivity in women, and the highest sensitivity recorded in men was 91·1% at an suboptimal efficiency of 86·0% (PRSm-1). In addition, no single Triage-only or Triage&Test approach approached the gold standard set by molecular-based testing. This underscores the challenges in implementing blended risk assessment and testing approaches that must balance diagnostic accuracy with practical usability and affordability across diverse settings.

Findings in wider context

A few studies in Sub-Saharan Africa only focused on risk stratification for the detection of CT, NG and/or TV infections[11,14,29]. However, while improved risk stratification and streamlining into testing could potentially reduce costs and the burden of STIs in high-prevalence settings through enhanced case detection, their effectiveness may rely on proper contextualization (e.g., selection of local risk factors), the local epidemic profile, and local adaptation, especially when integrating PRS-based risk assessment.

Recent focus on PRS tools for viral STIs, including acute and early HIV infection[12,13], highlights their potential to optimize resource allocation and detect infections that may otherwise be missed in routine settings. Despite growing interest in utilizing PRS tools and emerging statistical techniques for their development and validation[14,30–32], the integration of PRS tools into routine clinical practice remains slow. This gap underscores the need for implementation research to evaluate the practicality, logistics, costs, and effectiveness of PRS tools in everyday healthcare settings. Furthermore, deploying multiple PRS tools for different STIs simultaneously could be challenging for healthcare workers and overwhelming for patients. Integration of digital health interventions, such as specialized gadgets that assess risk factors for multiple diseases (e.g., acute HIV infection, NG, and CT/NG/TV infections), across diverse populations and clinical settings, could address these challenges[33–35]. Additionally, PRS tools may enhance client self-assessment and be used in community-based programmes, as suggested in studies on acute HIV infection[36], though further validation in non-clinical settings, like the broader community, is essential. An integrated approach to detecting both viral and bacterial STIs appears utmost crucial for epidemic control in settings like Southern Africa, where some populations such as women face a persistently high burden of STI and HIV co-infections[37].

Importantly, it also appeared feasible to increase access to molecular-based testing for the detection of bacterial STIs in resource-poor settings. For instance, a population-specific optimized pooling algorithm has been developed in Zambia for the detection of CT and NG infection using the GeneXpert platform with cost per sample tested being reduced from about $18 to $9·43[29].

STI care should be tailored to the epidemiological context and the pathogen, particularly in asymptomatic populations. While routine and large-scale testing for HIV and syphilis, two diseases with significant public health impact, is well-supported in Africa and plays a crucial role in epidemic control, the evidence for routine risk assessment and testing of asymptomatic populations for other STIs remains weak[38]. Testing for CT and NG in asymptomatic populations may result in only marginal reductions in incidence while increasing the risk of antibiotic overprescription that can lead to side effects and contribute to the development of AMR in both the targeted and non-targeted organisms[38].

Limitations and strengths

One limitation is the reliance on self-reported data, which can introduce bias and affect the accuracy of risk assessments and PRS tools. Moreover, developing pathogen-specific PRS tools could enhance accuracy but was beyond our scope, as we compared approaches to the syndromic standard of care. Lastly, the risk assessment algorithm was not prospectively applied but simulated using retrospective data from a cross-sectional study. Prospective validation is needed to confirm its feasibility and diagnostic performance in real-world settings.

A strength of this study is its comprehensive approach to evaluating various combinations of risk assessment and testing approaches, thus offering insights into the potential utility and limitations of these methods, particularly in populations of Southern Africa that face a high burden of CT/NG/TV infections[39–41]. In addition, the models for the PRS tools were developed using observed outcomes and internally validated through cross-validation and LASSO regression, ensuring analytical rigour and real-world applicability in settings with limited diagnostic capacity. Our study contributes to policy discussions on how the integration of adapted risk assessment and testing may enhance STI care quality. This is crucial while awaiting access to affordable and improved testing technologies in resource-poor settings.

Conclusions

Contextualized PRS tools in hypothetical one-step Triage&Test approaches improved STI care quality and efficiency but showed limitations among women, requiring cautious, context-specific implementation with ongoing evaluation. More research is needed to address implementation issues. Continued efforts to improve access to affordable STI diagnostic tests remain essential.

Data availability

The datasets generated and/or analysed during the current study are not publicly available because data sharing was not mentioned in the consent form for study participation but are available from the corresponding author on reasonable request.

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Author contributions

BK and IC directly accessed and verified the data reported in this manuscript. All authors had full access to the study data, contributed to the data interpretation, reviewed the manuscript and approved the final version. All authors also accept responsibility to submit for publication. BK contributed to the conceptualisation of this study, methodology, investigation, resources, data analysis, writing of the original draft, data visualisation, and supervision. BK also performed the statistical analysis. SL contributed to the investigation, data set-up and data curation, data analysis. NN contributed to the conceptualisation of the study, investigation, data analysis and supervision of the laboratory part of the study. EM contributed to the investigation, data curation, and overall supervision of study implementation. MD and EM contributed to the conceptualisation of this study, supervision, and investigation. MIM contributed to the conceptualisation of this study, data set-up, data curation and data analysis. MM, SM, SD, LD, NM, RDLT, HK, NS, MH, PV contributed to the conceptualization of this study, methodology, guidance on implementation and data analysis. AC and LTT contributed to the conceptualisation of this study, methodology, data analysis, and supporting the writing of the original draft. IC contributed to the conceptualisation of this study, methodology, investigation, resources, and data analysis.

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Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

This study was conducted in full compliance with the ethical principles outlined in the Declaration of Helsinki. Additionally, it adhered to all applicable national guidelines, including the approval of the Eswatini Health and Human Research Review Board (EHHRRB096/2021) and the Médecins Sans Frontières (MSF) Ethics Review Board (ID:2154). Written informed consent was obtained from all participants prior to study enrolment.

Additional information

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