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SUPPLEMENT ARTICLE

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Management algorithms for cervical cancer screening and precancer treatment for resource-limited settings

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Abstract

Management algorithms for screen-positive women in cervical cancer prevention programs have undergone substantial changes in recent years. The WHO strongly recommends human papillomavirus (HPV) testing for primary screening, if affordable, or if not, then visual inspection with acetic acid (VIA), and promotes treatment directly following screening through the screen-and-treat approach (one or two clinic visits). While VIA-positive women can be offered immediate ablative treatment based on certain eligibility criteria, HPV-positive women need to undergo subsequent VIA to determine their eligibility. Simpler ablative methods of treatment such as cryotherapy and thermal coagulation have been demonstrated to be effective and to have excellent safety profiles, and these have become integral parts of new management algorithms. The challenges faced by low-resource countries are many and include, from the management perspective, identifying an affordable point-of-care HPV detection test, minimizing over-treatment, and installing an effective information system to ensure high compliance to treatment and follow-up.

KEYWORDS

Cervical cancer; Low-resource setting; Management algorithms; Positive screening test; Screen and treat; Triaging

1 | INTRODUCTION

During the late 20th century, considerable reduction in cervical cancer incidence and mortality was achieved in high-resource countries owing to the systematic implementation of cytology-based cervical cancer screening programs (Pap smears), using a population-based approach.[1] These programs rely on frequently repeated cytology screening because of the low sensitivity of the method, and multiple visits are required for disease confirmation (by colposcopy and/or histopathology), treatment, and follow-up. Low- and middle-income countries (LMICs) have not been able to implement such a logistically complex model because of under-developed health systems—including a lack of laboratory infrastructure and human resources—and consequently are burdened with 86.5% of the deaths from cervical cancer worldwide.[2] Human papillomavirus (HPV) DNA testing has been recommended recently by the WHO as the first choice for primary screening for cervical cancer because of the objective nature of the test, its high-throughput capability, excellent reproducibility, and high negative predictive value, which allows extension of the screening interval to beyond 5 years.[3] A few high-resource countries in Europe have already replaced cytology with HPV testing in their screening programs.[4] In LMICs the use of HPV testing remains limited to small-scale demonstration projects because of high costs and the need for at least modest laboratory facilities.[5–7] Availability of less expensive, point-of-care HPV tests is likely to improve the uptake of the test in LMICs in the near future. The WHO has recommended visual inspection with acetic

acid (VIA) as the second-best screening test for low-resource settings, and more than 25 countries have introduced VIA in national screening programs, while many more are conducting pilot programs.[8]

With introduction of these newer screening tests, novel management algorithms for screen-positive women have also been investigated and recommended. Key goals are to limit the number of visits to health facilities and to ensure high compliance with treatment for women with cervical lesions. This is most relevant in low-resource settings, where women must overcome huge social and economic barriers to reach screening or treatment clinics and are likely to have only a once-in-a-lifetime opportunity to access services.[9] Algorithms include the following, which are discussed in the next sections—screen-positive women can be: (1) referred for diagnosis confirmation by colposcopy (a traditional practice in cytology-based programs); (2) triaged by a second test before referral; or (3) treated immediately for suspected premalignant lesions (Fig. 1). The comparison of the different algorithms with regard to their referral rates and efficacies to detect or prevent cervical intraepithelial neoplasia (CIN) 3+ disease is shown in Table 1.

2 | REFERRAL TO CONFIRMATORY COLPOSCOPY

The standard of care for cytology-based programs in high-resource countries has been colposcopic verification and localization of disease in screen-positive women. However, facilities for colposcopy are limited in low-resource settings because the specialized and expensive equipment is difficult to procure and maintain, the training requirements for providers are high, and the necessary histopathology services are rarely available. As a consequence, the new management algorithms of screen-positive women in LMICs aim to minimize the use of colposcopy, but some discussion of the method is included in this review.

In addition to the logistical challenges, colposcopy in noncytology-based programs is more challenging, as the colposcopist often relies on the cytology result to diagnose the morphological abnormality.[10] Highly-sensitive HPV tests can detect potential CIN 2 or CIN 3 at very early stages, when the lesions are too small or subtle to be recognized visually.[11] In the atypical cells of undetermined significance, low-grade squamous intraepithelial lesion (ASCUS-LSIL) Triage Study (ALTS), the sensitivity of baseline colposcopy for the subsequent detection of CIN 3+ was only 53%.[12] In a randomized controlled trial in India, the risk of invasive cancer among VIA-positive women with apparently normal colposcopy and histopathology during 12 years of follow-up was much higher than that of VIA-negative women (hazard ratio 6.5; 95% CI, 1.6–27.1).[13] The risk was similar to that observed in VIA-positive women with colposcopically detected abnormalities who did not undergo biopsy or treatment, thus demonstrating the futility of colposcopy in this scenario.

Another major limitation of colposcopy as a triaging technique is its low specificity, which is approximately 50% for detecting high-grade cervical lesions, even in experienced hands.[14] The specificity can

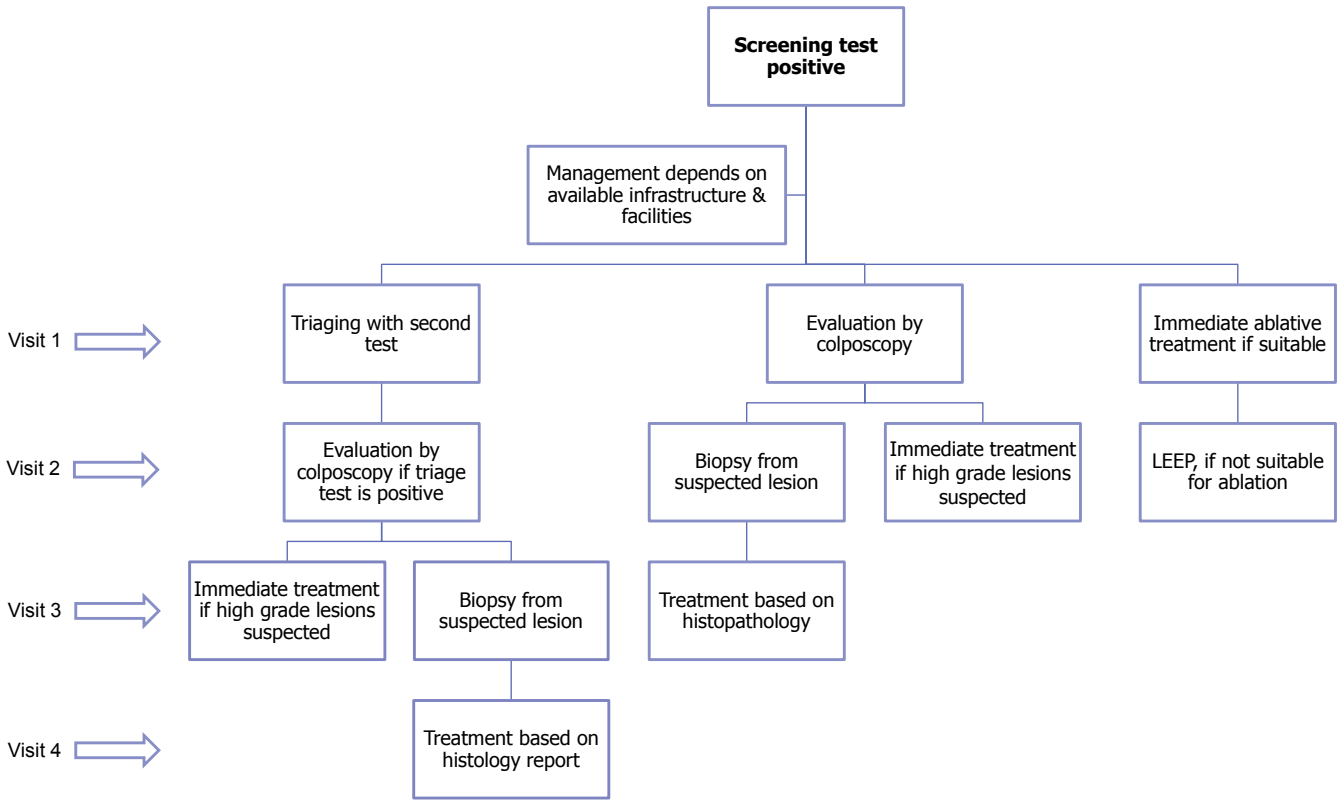

FIGURE 1 Summary of management options for screen-positive women. Screening and treatment can be completed in a single visit if there is a point-of-care screening test and the lesion is suitable for ablative treatment with a simpler method such as cryotherapy or thermal coagulation. [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Comparison of different management algorithms of screen-positive women by referral rates and their efficacies to detect or prevent CIN 3+ disease.

Management algorithms for screen-positive women	Author	Number of screen-positive women undergoing specified management	Referral rate (to colposcopy or treatment)	Sensitivity to detect CIN 3+	Percentage of CIN 3+ prevented at 36 months
Triaging of ASCUS cytology by HPV test	ASCUS-LSIL Triage Study Group, 2013[12]	1161	53.1%	92.4% (95% CI, 88.7–95.2)	–
Triaging of ASCUS cytology by repeat cytology (2 visits at 6 months interval) at ASCUS threshold	ASCUS-LSIL Triage Study Group, 2013[12]	1164	67.1%	95.4% (95% CI, 91.4–99.3)	–
Referral of ASCUS cytology to immediate colposcopy	ASCUS-LSIL Triage Study Group, 2013[12]	1163	100%	53.6% (95% CI, 43.2–63.8)	–
Triaging of HPV-positive women by cytology (ASCUS threshold)	Muwonge et al. 2014[26]	2922	38.2%	78.5% (95% CI, 70.6–85.1)	–
Triaging of HPV positive women by VIA	Muwonge et al. 2014[26]	2922	41.2%	83.5% (95% CI, 76.1–89.3)	–
Triaging of HPV positive women by HPV genotyping (types 16/18)	Castle et al. 2011[53]	3502	27.6%	59.5% (95% CI, 53.4–65.4)	–
Referral of HPV positive women to colposcopy	Basu et al. 2015[6]	1394	100%	93.8% (95% CI, 88.9–97.0)	–
Referral of HPV positive women to cryotherapy	Denny et al. 2010[37]	465	100%	–	77.4% (95% CI, 61.8–92.9
Referral of VIA-positive women to colposcopy	Basu et al. 2015[6]	2818	100%	69.8% (95% CI, 62.1–76.7)	
Referral of VIA-positive women to cryotherapy	Denny et al. 2010[37]	482	100%		38.1% (95% CI, 8.4–67.8)

be even lower when the specificity of the primary screening test is low, as is the case with the HPV test or VIA.[15] In a large community-based study in India, colposcopy was used to triage VIA and/or HPV positive women.[16] Colposcopy falsely suspected abnormalities in 68.8% of women with normal histopathology. A systematic, pooled analysis of the accuracy of colposcopy observed that for every 1000 screen-positive women referred for colposcopy, 464 would be falsely diagnosed to have CIN 2/CIN 3 and would be unnecessarily treated (in a "colposcopy-and-treat" scenario).[17] Based on such evidence, WHO has recommended direct referral of screen-positive women to treatment, bypassing colposcopy, a process now known as "screen and treat".[18]

3 | TRIAGING OF HPV-POSITIVE WOMEN

As noted above, a major disadvantage of HPV testing is its low specificity—most infected women will clear the infection within 1–2 years and will not develop disease.[19] The pooled estimated specificity of HPV testing from 15 studies involving 45 783 participants was 88%, which implies that the test will be falsely positive in 12 out of every 100 normal women.[17] A risk stratification of HPV-positive women is needed to decide on further management, and several triaging strategies have been evaluated. Cytology is the most widely recommended test to triage HPV-positive women—where quality-assured cytology is available.[20] HPV-positive women with a cytology diagnosis of ASCUS or worse are referred for colposcopy, and the rest are advised to have repeat HPV testing after 1 year. Cytology performs better in a triaging scenario, since the prevalence of disease is high in the sample and cytologists have a limited number of specimens to evaluate. There is evidence that the competency of cytologists improves with prior knowledge of HPV status.[21]

HPV-positive women may be further tested to know if they are positive for the most carcinogenic types, HPV 16 and 18, and such information can be used to triage these women to colposcopy. Due to such differential risks, genotyping for HPV 16/18 has been evaluated as a triaging test for women with nonspecific HPV-positive results.[22] The advantages are that the test is more reproducible than cytology, the original cervical sample can be used for triaging, and the test can be provided concurrently with the pooled detection of other carcinogenic HPV genotypes (e.g. Cobas test [Roche Molecular Systems, Branchburg, NJ, USA], Xpert HPV test [Cepheid, Sunnyvale, CA, USA]). In evaluation studies, the risk of high-grade CIN in HPV 16/18 positive women exceeded that in nontyped HPV-positive women with ASCUS cytology, signifying the need for colposcopy referrals of these

women.[23,24] The current recommendations by the American Society for Colposcopy and Cervical Pathology (ASCCP) are direct referral to colposcopy for HPV 16/18 positive women and repeat testing after 1 year for women positive for other HPV types.[25] In resource-constrained settings the practicality of recalling the women who are HPV 16/18 negative but positive for other oncogenic types should be carefully considered, as these women still have higher risk of having high-grade lesions compared with the HPV-negative women.

Unfortunately, in resource-constrained settings neither cytology nor HPV genotyping may be feasible. WHO recommends VIA for triaging HPV-positive women in such settings. The test characteristics of VIA generally improve when performed on a limited number of women with high prevalence of disease in a triage setting. In a community-based multicenter study in India, the colposcopy referral rates for VIA triage and cytology triage (at ASCUS threshold) were similar (41.2% vs 38.2%), with comparable sensitivities of CIN 2/CIN 3 (81.9% vs 84.0%).[26] The other advantages of VIA triaging are that it is a point-of-care test, and it can determine whether ablative treatment is appropriate, which allows treatment of a woman at the same visit. However, VIA performance is very variable across settings, and the sensitivity can be very low. There is a concern that HPV testing followed by VIA triage can compromise the sensitivity of the original test and offset the benefit of a lower referral rate by missing lesions. Direct referral of all HPV-positive women to colposcopy or treatment may be a better strategy, if good quality VIA testing cannot be assured.

Certain novel biomarkers have also been studied to triage HPV-positive women. These are dual staining by $p16^{ink4a}$ (a cyclin-dependent kinase inhibitor that is markedly overexpressed in transforming HPV infections), Ki-67 (a cell-proliferation marker), and methylation markers (CADM1, MAL and miR-124-2).[27–29] Using these markers requires numerous resources and thus, they are not yet considered suitable for LMICs. However, a rapid and logistically simple test—the OncoE6 (Arbor Vita, Fremont, CA, USA)—to detect the expression of the E6 oncoprotein of HPV high-risk types 16, 18, 31, 33, and 45 is being evaluated in the multicenter ESTAMPA study in several Latin American countries as a potentially suitable triaging test for LMICs.[7] In a preliminary study in China the test had lower sensitivity (42.8%) but higher specificity (94.3%) compared with HPV genotyping to detect CIN 2+ disease in HPV-positive women.[30]

4 | TRIAGING OF WOMEN WITH MINOR CYTOLOGICAL ABNORMALITIES

Some of the middle-income countries like Thailand and Sri Lanka have reorganized their screening programs by improving cytology capacity. Women with a cytological diagnosis of ASCUS have very low risk of having high-grade CIN, and the majority of these abnormalities regress spontaneously. In a study by the Kaiser Permanente Northern California (KPNC) Health System, the 5-year cumulative risk of CIN 2+ disease among women aged 30–64 years for baseline cytology of ASCUS was just 6.9%.[31] Unnecessary referral to colposcopy of women with regressive lesions not only overburdens the health system but also causes over-treatment (with resultant complications) and anxiety to patients. The ALT study noted above was a multicenter, randomized trial that evaluated three alternative strategies to manage women with ASCUS cytology—immediate colposcopy, repeat cytology, or triage by high-risk HPV DNA test.[32] HPV testing identified 96% of women with CIN 3+, while referring 56% of the women to colposcopy; repeat cytology using a triage threshold of ASCUS identified 85% of women with CIN 3+, while referring 58% women to colposcopy. Repeat cytology also resulted in a delay in referral by at least 6 months and may affect compliance. Subsequent meta-analyses of triaging strategies for ASCUS results clearly demonstrated the higher sensitivity of HPV testing over cytology with similar referral rates, which has led to the acceptance of HPV testing as the standard of care for triaging of ASCUS results in high-resource settings.[25,33]

5 | STRATEGIES TO REDUCE THE NUMBER OF CLINIC VISITS

One of the major barriers to the success of cervical cancer screening programs is the failure of screen-positive women to complete diagnosis and treatment. This problem is common in LMICs, as women cannot afford to travel to health facilities multiple times because of social and economic constraints, and effective tracking of patients is not feasible owing to poor health information systems. Compliance with treatment can be improved by reducing the number of visits through either of the following strategies.

5.1 | Colposcopy-and-Treat Approach

In a colposcopy-and-treat approach, women reporting for colposcopy with abnormal screening tests are offered treatment at the same visit if the colposcopist suspects high-grade abnormalities. This improves patient compliance, reduces treatment cost, and causes less emotional stress for women. This approach is being used successfully in the VIA screening program in Bangladesh, where it significantly improved treatment compliance of nearly half of women with colposcopically suspected high-grade lesions who had CIN 2+ disease on histopathology.[34] More than 90% of women accepted treatment during the colposcopy visit. The risk of overtreatment and the resultant complications are far outweighed by the risk of the women with high-grade lesions remaining untreated and subsequently developing invasive cancer. In a rural, community-based setting in India, trained nurses performed colposcopy and cryotherapy on VIA-positive women.[35] Nearly 75% of eligible women accepted treatment at the same visit; of these, 55.6% had CIN on histopathology and only 0.5% of the treated women with CIN had subclinical invasive cancer detected on subsequent histopathology.

5.2 | Screen-and-Treat Approach

Treatment of screen-positive women (screen-and-treat approach) without colposcopic or histopathologic verification is the most

effective strategy to improve compliance, as this involves the least number of visits (Fig. 1). If screening and treatment are completed at the same sitting, this is known as the single-visit approach. The screen-and-treat strategy can be used in both VIA- and HPV-testing programs and usually involves treatment by an ablative technique. For ablative treatment, the cervical squamocolumnar junction (SCJ) should be located on the ectocervix, the lesion should occupy less than 75% of the surface of the cervix, and there should be no suspicion of invasive cancer.[3] For VIA, these characteristics are assessed during the procedure itself, when 3%–5% acetic acid is applied to the cervix and lesions are revealed as tissue that appears white. The suitability for ablative treatment for the HPV-positive woman is assessed by similar application of 3%–5% acetic acid on the cervix and the same criteria as above are applied or there is no visible lesion. The women not eligible for ablative treatment are referred for excisional treatment.

The evidence for the strong recommendation of the screen-and-treat strategy by WHO was derived from a South African randomized controlled study, in which VIA- or HPV-positive women suitable for ablative treatment were treated with immediate cryotherapy in the study arm.[36,37] In the control arm the screen-positive women were not treated immediately but had colposcopic evaluation after 6 months. Compared with the control arm, the treated HPV arm reported a 77% reduction of CIN 3+ lesions and the treated VIA arm a 38% reduction over 3 years of follow-up, suggesting high protection offered by such a simple algorithm. The benefits far outweigh the potential harms (discussed later) of overtreatment.

Cryotherapy of cervical premalignant lesions is highly effective, with reported cure rates of 90% for any CIN and 70% for CIN 3 disease even in a primary care setting.[38,39] Thermal coagulation (also known as cold coagulation) is as effective as cryotherapy to treat CIN and both techniques have excellent safety profiles even when performed by nonphysician providers.[40] The VIA screen-and-treat strategy has been used successfully to screen large numbers of women in the cervical cancer screening program in Zambia, with 56.4% of VIA-positive women being eligible for cryotherapy and 87% of the eligible women accepting same-day treatment.[41] In a rural setting in Malawi, VIA-positive women were offered thermal coagulation at the screening visit. Out of the 429 VIA-positive women suitable for ablative treatment, 361 (84.1%) received treatment on the same day, with a very high cure rate (>90%) observed at 3–6 months follow-up.[42] In a demonstration project in El Salvador, HPV-positive women were offered either same day treatment or referral for colposcopy and treatment based on histopathological diagnosis. In the first group, 88% of women completed treatment, while in the colposcopy group only 44% of women were compliant with all the required visits, thus strongly underscoring the fact that effective linkage between screening and treatment can be best achieved with strategies involving the minimum number of visits.[5]

Some of the practical problems limiting the implementation of the screen-and-treat strategy are the costs of overtreatment (both financial and personal), national regulations that do not allow nonphysician providers to perform treatment, need for training large number of providers, and sustaining cryotherapy in a primary care setting.[43]

6 | COST-EFFECTIVENESS OF DIFFERENT MANAGEMENT ALGORITHMS

Evidence from economic evaluation studies comparing methods for cervical cancer screening has been fairly consistent in showing that screening strategies that increase coverage and/or require fewer visits (thereby reducing loss to follow-up of screen-positive women) tend to be more cost-effective. One of the earliest cost-effectiveness studies was conducted in South Africa using mathematical modelling, and showed that a strategy of VIA or HPV testing followed immediately with cryotherapy was more cost-effective than strategies using conventional cytology.[44] A subsequent analysis by the same group using the same approach comparing screening strategies that could be performed at primary care health facilities in five LMICs largely confirmed these results.[45] Screen-and-treat approaches with VIA or HPV testing at the age of 35 years, with screening two or three times in a lifetime (depending on the country), were considered more cost-effective compared with cytology screening requiring three visits. Similar observations were made in studies conducted in El Salvador and China.[46,47]

Trade-offs between loss to follow-up and other characteristics of screening programs—including coverage and test sensitivity—were examined in another study.[48] Values for test sensitivity and loss to follow-up were the most influential factors when comparing one-visit VIA to two-visit HPV testing. One-visit VIA was only attractive when loss to follow-up exceeded 60%.

For many LMICs, establishing and sustaining a quality cervical cancer screening program may pose a considerable burden on the health budget. The estimated total cost of cervical cancer screening, diagnostic testing, and treatment of precancerous lesions from 2015 to 2024 for 102 LMICs ranges between US $5.1 billion and US $42.3 billion, depending on the screening scenario, the intensity of screening, and the speed at which the program is rolled out.[49] The third edition of the *Disease Control Priorities Project* recommends opportunistic rather than organized screening with VIA or HPV testing and treatment of precancerous lesions as part of an essential package of health interventions in low-income countries, owing to the high cost of organized population-based screening programs.[50] While LMICs with high cervical cancer burden should make every effort to implement cervical cancer screening, facilities for early diagnosis of cervical cancer in symptomatic women combined with accessible, affordable, and effective treatment also need to be strengthened to improve the stage at presentation of cervical cancer and reduce mortality from the disease.

7 | OUTSTANDING CHALLENGES

Even though the alternative screening and management algorithms discussed here have simplified the logistics of cervical cancer

screening, implementation of the programs in LMICs is limited for several reasons. Among these are the needs to optimize fiscal and human resources, mobilize and educate communities, organize services that meet women's needs and preferences, and strengthen health information systems to track screen-positive women for follow-up. A truly point-of-care and affordable HPV test is still elusive. The higher specificity of HPV E6 oncoprotein detection observed in initial studies is encouraging and needs further evaluation. The real program effectiveness of the single-visit screen-and-treat algorithm should be studied further in the countries that have implemented such a strategy. Where single-visit approaches are not feasible, strategies for improving follow-up (such as mobile phone reminders and outreach treatment services) should be evaluated.

An additional future consideration for screening and management is the advent of highly effective HPV vaccines, first against HPV 16 and 18, and now against additional high-risk types. Over a relatively short period, more than 80 countries or territories have introduced HPV vaccination into their national immunization programs, and 33 of these are LMICs, with many more implementing pilot projects.[51] The impact of large-scale HPV vaccination will be an eventual drastic reduction in the prevalence of disease, accompanied by a decline in both sensitivity and positive predictive value of cytology and VIA.[52] Furthermore, the early vaccines targeted just HPV 16 and 18, and the high-grade premalignant lesions caused by other oncogenic HPV types may have a more indolent natural history and may require a different management approach. These questions will pose new challenges for screening and management in LMICs and will need the attention of the research community.

AUTHOR CONTRIBUTIONS

PB and RS conceived the article, reviewed the evidence, and wrote the manuscript. FM, YC, RH, and FZ assisted in reviewing the evidence and writing the manuscript.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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