RESEARCH ARTICLE

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Treatment methods for cervical intraepithelial neoplasia in England: A cost-effectiveness analysis

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Abstract

Objective: To compare the cost-effectiveness of different treatments for cervical intraepithelial neoplasia (CIN).

Design: A cost-effectiveness analysis based on data available in the literature and expert opinion.

Setting: England.

Population: Women treated for CIN.

Methods: We developed a decision-analytic model to simulate the clinical course of 1000 women who received local treatment for CIN and were followed up for 10 years after treatment. In the model we considered surgical complications as well as oncological and reproductive outcomes over the 10-year period. The costs calculated were those incurred by the National Health Service (NHS) of England.

Main outcome measures: Cost per one CIN2+ recurrence averted (oncological outcome); cost per one preterm birth averted (reproductive outcome); overall cost per one adverse oncological or reproductive outcome averted.

Results: For young women of reproductive age, large loop excision of the transformation zone (LLETZ) was the most cost-effective treatment overall at all willingness-to-pay thresholds. For postmenopausal women, LLETZ remained the most cost-effective treatment up to a threshold of £31,500, but laser conisation became the most cost-effective treatment above that threshold.

Conclusions: LLETZ is the most cost-effective treatment for both younger and older women. However, for older women, more radical excision with laser conisation could also be considered if the NHS is willing to spend more than £31,500 to avert one CIN2+ recurrence.

KEYWORDS
ablation, conisation, cost-effectiveness, excision, LLETZ, preterm birth, recurrence

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1 | INTRODUCTION

There are two broad strategies for the local treatment of cervical intraepithelial neoplasia (CIN): excisional and ablative treatments. Excisional techniques include cold knife conisation (CKC), laser conisation, needle excision of the transformation zone (NETZ), Fischer cone biopsy excision (FCBE) and large loop excision of the transformation zone (LLETZ). Ablative techniques include radical diathermy, laser ablation, cold coagulation (also known as thermal ablation) and cryotherapy. The choice of technique varies within the UK and across different countries. In the UK, LLETZ is the preferred treatment, with some units offering alternative techniques more frequently than others. This preference is because LLETZ is quick, is easy to perform and is low cost. In some countries, CKC is still regularly performed; in others, laser conisation or ablation is common practice.

Although complications from treatment were previously thought to be relatively mild and uncommon, an increasing body of retrospective observational studies and meta-analyses suggest that treatment, particularly excision, adversely affects future reproduction and the risk of prematurity.[1–4] The frequency and severity of the observed adverse events is higher for more radical techniques and with increasing cone length.[1,4–6] However, concerns have been raised that the progressive reduction in radicality of treatment has led to an increased risk of invasion in the years following the treatment.[7,8] A previously published Cochrane systematic review of randomised controlled trials reported no evidence of a difference in treatment failure rates among treatment techniques; this review, however, was grossly underpowered to detect the possibly small relative effects among the available treatments.[9]

We have recently published a network meta-analysis (NMA) assessing the comparative effectiveness and reproductive morbidity of various treatment techniques.[10] More radical treatments (such as CKC and laser conisation) were associated with a lower risk of treatment failure but a higher risk of preterm birth, as compared with less radical treatments (such as LLETZ and ablation). LLETZ achieved the optimal balance in the trade-off between treatment failure and preterm birth rates, although, ultimately, the choice of treatment should consider the woman's age, the location and severity of the lesion, and the woman's fertility wishes.

Although absolute risks may help with counselling and clinical decision making, the assessment of cost-effectiveness is important to inform public health policies and to optimise the allocation of healthcare resources. The aim of this study was to evaluate the cost-effectiveness of alternative local treatment techniques for CIN in England from the National Health Service (NHS) perspective, based on data published in our recent NMA.[10]

2 | METHODS

We developed a cost-effectiveness model that simulated the clinical course of women who received CIN treatment in England, over a 10-year period after treatment. We involved patient representatives in the design of this study and the prioritisation of the clinical questions.

2.1 | Population

Our population represented a simulated cohort of 1000 women with a median age of 30 years and a prior history of local surgical treatment for CIN2 or worse (CIN2+). The age profile of the cohort corresponded to that of women receiving CIN treatment in England, with the assumption that the age distribution of the treated women is the same as that of women with high-grade cytological abnormalities.[11] We only included women with type-1 or type-2 transformation zones.

2.2 | Treatment

The treatment modalities evaluated in the cost-effectiveness model were selected based on the findings of our previously published NMA,[10] and included CKC, laser conisation, laser ablation, cryotherapy and LLETZ; women treated with LLETZ had the endocervical canal removed in a single piece, and no women were treated with top-hat LLETZ. We selected LLETZ as the 'usual care' strategy (comparator), based on its high prevalence of use in England. Our analysis did not include radical diathermy, because this technique is no longer used, and nor did it include FCBE or NETZ, because these techniques were not evaluated in the NMA, owing to a lack of studies. Furthermore, we did not include cold coagulation in the main analysis because the data on cold coagulation from

the NMA were very limited; as a result of the limited data, we only included cold coagulation in a separate analysis, presented in Appendix S1.

2.3 | NHS clinical pathway

Our model (Figure 1) was informed by the NHS clinical pathway for post-treatment follow-up.[12] Treated women who failed the 'test of cure' at 6 months (i.e. women who tested positive for high-risk human papillomavirus, hrHPV+) had reflex cytology and colposcopy. Women who were hrHPV– were discharged and recalled at 3 years. We relied on the data from the NMA,[10] unpublished NHS audit data and expert opinion to estimate the probability of progression in the model.

2.4 | Outcomes

For our main analysis we considered oncological and reproductive outcomes (as defined in the NMA).[10] For oncological
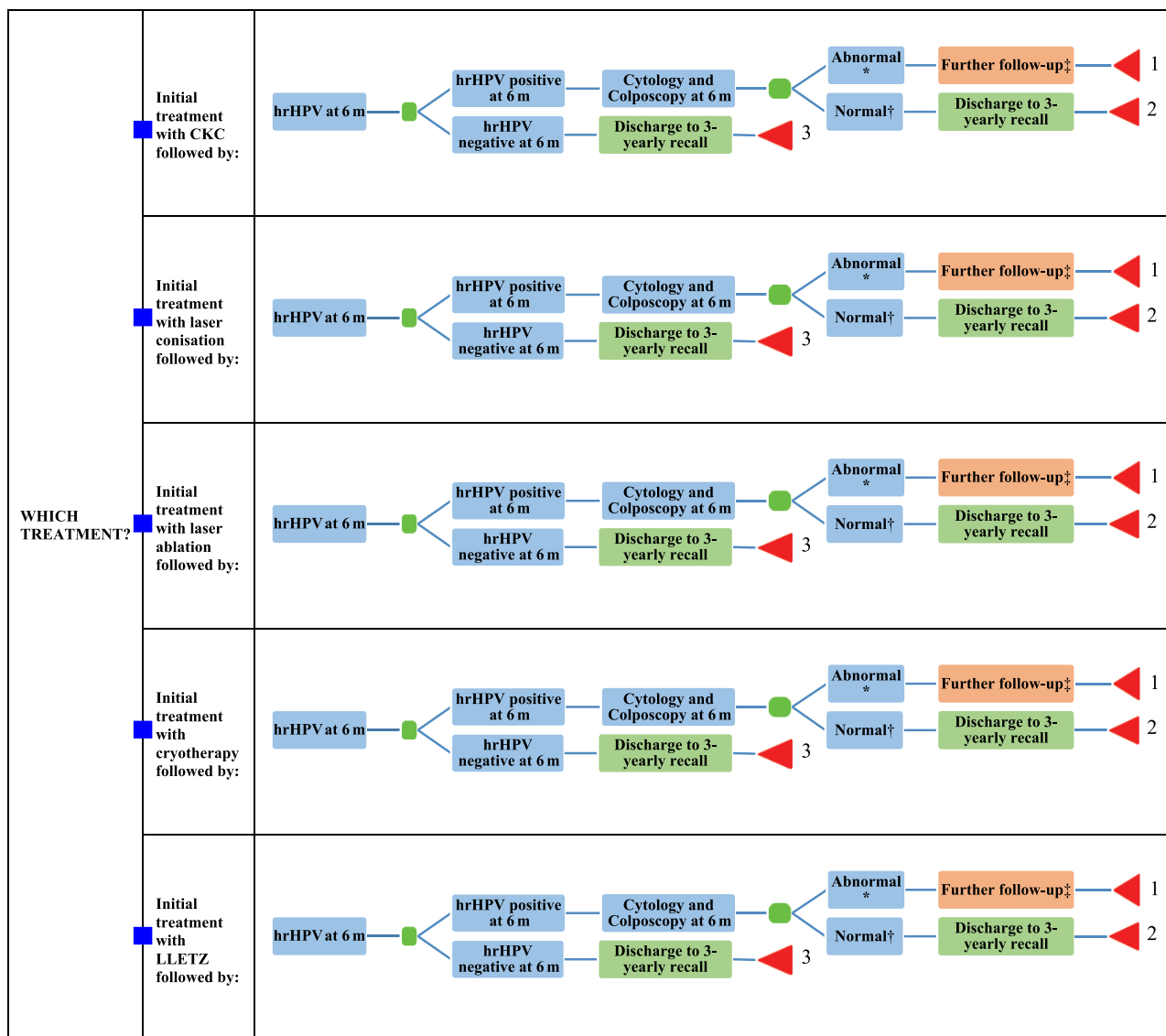

FIGURE 1 Decision tree model on post-treatment follow-up in the NHS. The blue square (choice node) represents the range of treatments from which a clinician might choose. The green shape (chance node) represents an event with multiple possible outcomes, each of which has a specific probability. The red triangle (terminal node) represents a pay-off (i.e. end point measured in terms of health effects and NHS costs). For costs of payoffs 1–3, see Table S1. For probability of hrHPV+ at 6 months (first chance node), see Table S2. In the second chance node, the probability of abnormal cytology or colposcopy was 20%, and the probability of normal cytology and colposcopy was 80% (audit data). *Cytological result of ASC-H+, colposcopic impression of CIN1+ or CIN1+ on biopsy (if biopsies were taken during colposcopy). †Cytological result of ≤LSIL, no colposcopic impression of CIN and no CIN on biopsy (if biopsies were taken during colposcopy). ‡Follow-up with hrHPV test, ±cytology, ±colposcopy, ±biopsies; repeat treatment when CIN2+ was diagnosed during follow-up (for total rates of CIN2+ after each technique, see Table S3). ASC-H, atypical squamous cells that cannot exclude high-grade squamous intraepithelial lesion; CIN, cervical intraepithelial neoplasia; CKC, cold knife conisation; hrHPV, high-risk human papillomavirus; LLETZ, large loop excision of the transformation zone; LSIL, low-grade squamous intraepithelial lesion; m, month(s); NHS, National Health Service.

outcomes we considered the risk of testing hrHPV+ at 6 months after treatment as well as the risk of CIN2+ over the following 10 years after treatment; histology was used in preference to cytology for the diagnosis of CIN2+, if possible. For reproductive outcomes we considered the risk of preterm birth in subsequent pregnancies after treatment, defined as delivery at <37 weeks of gestation, and we further divided preterm birth into moderate (32–36 weeks of gestation), severe (28–31 weeks of gestation) and extreme (<28 weeks of gestation) subcategories.

We elicited absolute rates with plausible ranges for the outcomes of interest from a group of three leading clinical experts (DL, MK and PMH) (Tables S2–S4). The experts gave their rates after assessing the results of the NMA, the results from articles of the highest quality (randomised or nonrandomised studies, selected according to the internal validity of the results, setting and sample size), and local and national audit data. They were also asked to provide an upper and lower bound of a plausible range; in the case of disagreement, consensus was reached after discussion. Expert opinion is considered a credible source of information for decision-analytic modelling if the required data are unavailable, are not applicable to the UK setting or are of suboptimal quality[13]; all three reasons applied here.

2.5 | NHS costs

The total cost of each treatment was the sum of the initial cost (including general anaesthesia and surgical complications), the cost of oncological outcomes and the cost of reproductive outcomes. Unit cost data for treatment with or without general anaesthesia, surgical complications, hrHPV test, cytology, consultation appointment, colposcopy, with or without biopsies, and pathology review were extracted from the literature (Table S1).[9,14–16]

For reproductive outcomes we assumed that the costs of prematurity were primarily concentrated on the (high) NHS costs for the initial years of life, and were mainly associated with the provision of neonatal intensive care for preterm infants and with early hospitalisation.[17] For each category of preterm birth, we assumed that 70% of cost was incurred in the first 2 years (40% in the first year and 30% in the second year) and the remaining 30% was incurred in the remaining 8 years (3.75% annually from the third year onwards), in accordance with previously published literature.[18] We assumed that women did not deliver any babies within the first year after treatment, given the common advice to avoid conception for the first 6 months and the average length of gestation. A cohort of treated women with a median age similar to that of women in our model had a fertility rate of 0.084 pregnancies per woman-year after treatment.[19] Given that no women delivered within the first year after treatment, we assumed that each woman had, on average, 0.76 live births in the

following 9 years. We also assumed that the pregnancies were equally distributed within this 9-year period.

For reproductive outcomes we only considered the additional cost per preterm infant as compared with term infants. Similarly, for oncological outcomes we did not consider the cost of routine screening after discharge.

2.6 | Cost-effectiveness analysis

We developed a decision tree model to estimate the costs and effects associated with different local treatment modalities for CIN (Figure 1). For each intervention we considered the number of events (outcomes) and the NHS costs for a population of 1000 women (for a 10-year period). We calculated the incremental cost-effectiveness ratio (ICER) by dividing the difference in total costs (incremental cost) by the difference in outcomes (incremental effect) to provide a ratio of 'extra NHS cost to be invested per extra unit of health effect gained'.[20] We expressed the results as: (i) extra NHS costs per one additional hrHPV+ test averted at 6 months after treatment; (ii) extra NHS costs per one additional CIN2+ case averted over the 10-year period; (iii) extra NHS costs per one additional preterm birth averted over the 10-year period; and (iv) extra NHS costs per one additional CIN2+ case or preterm birth averted over the 10-year period (composite outcome). We reported ICERs for each treatment modality compared with LLETZ. For the 10-year time horizon of our model, we discounted all future costs and outcomes at 3.5% per year, as recommended by the National Institute for Health and Care Excellence (NICE).[21]

To take the uncertainty of costs and expert estimates into account, we performed probabilistic sensitivity analyses, as recommended by NICE.[21] We assumed a normal distribution for outcomes and a log-normal distribution for costs. We created cost-effectiveness acceptance curves to calculate the probability of cost-effectiveness for different treatments at various willingness-to-pay thresholds. We also created cost-effectiveness planes (with LLETZ as reference); the willingness-to-pay threshold was set at £25,000.[21] We performed probabilistic sensitivity analyses using the *cea* and *cea_pw* functions of the *hesim* package in R 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).[22,23]

2.7 | Additional analyses

In the main analysis we assumed that each woman had, on average, 0.76 live births after treatment. In a separate analysis we assumed that each woman had, on average, 1.61 live births after treatment (equal to the total fertility rate in England and Wales).[24] Finally, in another analysis we assumed that all treated women were postmenopausal and had no live births.

3 | RESULTS

The total average NHS costs per treated woman over a 10-year period were: £1245 (plausible range, £976–£1516) for LLETZ; £1258 (£856–£1667) for cryotherapy; £1607 (£1280–£1937) for laser ablation; £1975 (£1605–£2345) for laser conisation; and £2642 (£2308–£2978) for CKC. The major contributor to the overall cost was the cost of the management of preterm births (Figure 2). Compared with LLETZ, treatments with higher preterm birth rates (i.e. CKC and laser conisation) were associated with a substantially higher cost. On the other hand, treatments with lower preterm birth rates (i.e. laser ablation and cryotherapy) were associated with a marginally higher cost, owing to higher treatment failure rates that pushed up the total cost.

To avert one hrHPV+ test at 6 months after treatment, the NHS would have to invest £72,568 and £24,936 more for CKC and laser conisation, respectively, using LLETZ as the reference (i.e. ICER = £72,568 and £24,936 for CKC and laser conisation, respectively). To avert one CIN2+ case over the 10-year period after treatment, the NHS would have to invest even more money, as ICER (vs LLETZ) was £102,474 for CKC and £49,655 for laser conisation. Laser ablation and cryotherapy had negative ICERs (vs LLETZ) for both oncological outcomes. For preterm birth (<37 weeks of gestation), ICER (vs LLETZ) was £37,327 for laser ablation and £2934 for cryotherapy, whereas CKC and laser conisation had negative ICERs. When we considered both CIN2+ cases and preterm births as a composite outcome, all treatments had negative ICERs (vs LLETZ).

When the outcome of interest was the avoidance of one hrHPV+ test at 6 months, probabilistic sensitivity analyses found that LLETZ had the highest probability of being the most cost-effective treatment up to a willingness-to-pay threshold of £25,000, but laser conisation had the highest probability of being the most cost-effective treatment above

that threshold (Figure 3A). When the outcome of interest was the avoidance of one CIN2+ case over the 10-year period, LLETZ had the highest probability of being the most cost-effective treatment up to a willingness-to-pay threshold of £50,000, but laser conisation had the highest probability of being the most cost-effective treatment above that threshold (Figure 3B). When the outcome of interest was the avoidance of one preterm birth, cryotherapy had the highest probability of being the most cost-effective treatment at all thresholds (Figure 3C). However, when we considered both preterm births and CIN2+ cases, LLETZ had the highest probability of being the most cost-effective treatment at all thresholds (Figure 3D). Cost-effectiveness planes are shown in Figure S1.

In a separate analysis we also included cold coagulation, but the data on cold coagulation were very limited. We found that cold coagulation was the most cost-effective treatment at all thresholds in terms of reproductive outcomes (Figure S2C). However, LLETZ remained the most cost-effective treatment at all thresholds when we considered both preterm births and CIN2+ cases (Figure S2D).

In the above-mentioned analyses we assumed that each woman had, on average, 0.76 live births. In a separate analysis we assumed that each woman had, on average, 1.61 live births. In that case, cryotherapy was the treatment with the lowest total cost, followed by LLETZ (Figure S3B). However, the results of the probabilistic sensitivity analyses did not materially change, and LLETZ remained the most cost-effective treatment at all thresholds when CIN2+ cases were combined with preterm births (Figure S4D). Cost-effectiveness planes are shown in Figure S5. In a separate analysis we assumed that all women were postmenopausal and that no pregnancies occurred. In that case, LLETZ was the treatment with the lowest total cost, followed by cryotherapy (Figure S3C). Probabilistic sensitivity analyses found that LLETZ was the most cost-effective treatment for hrHPV+ and CIN2+ up to thresholds of £16,000 and £31,500, respectively, but that laser
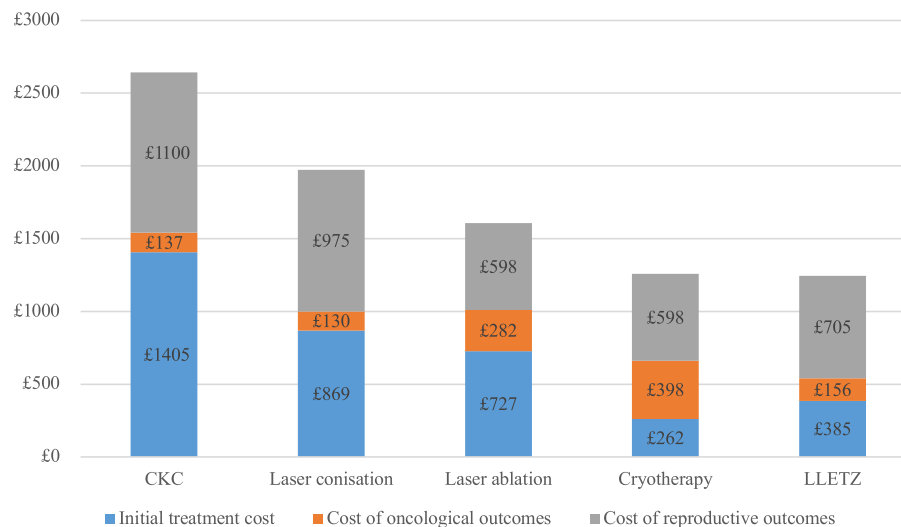

FIGURE 2 Breakdown of average NHS cost per treated woman over the 10-year period (on the assumption that each woman had, on average, 0.76 live births). CKC, cold knife conisation; LLETZ, large loop excision of the transformation zone; NHS, National Health Service.
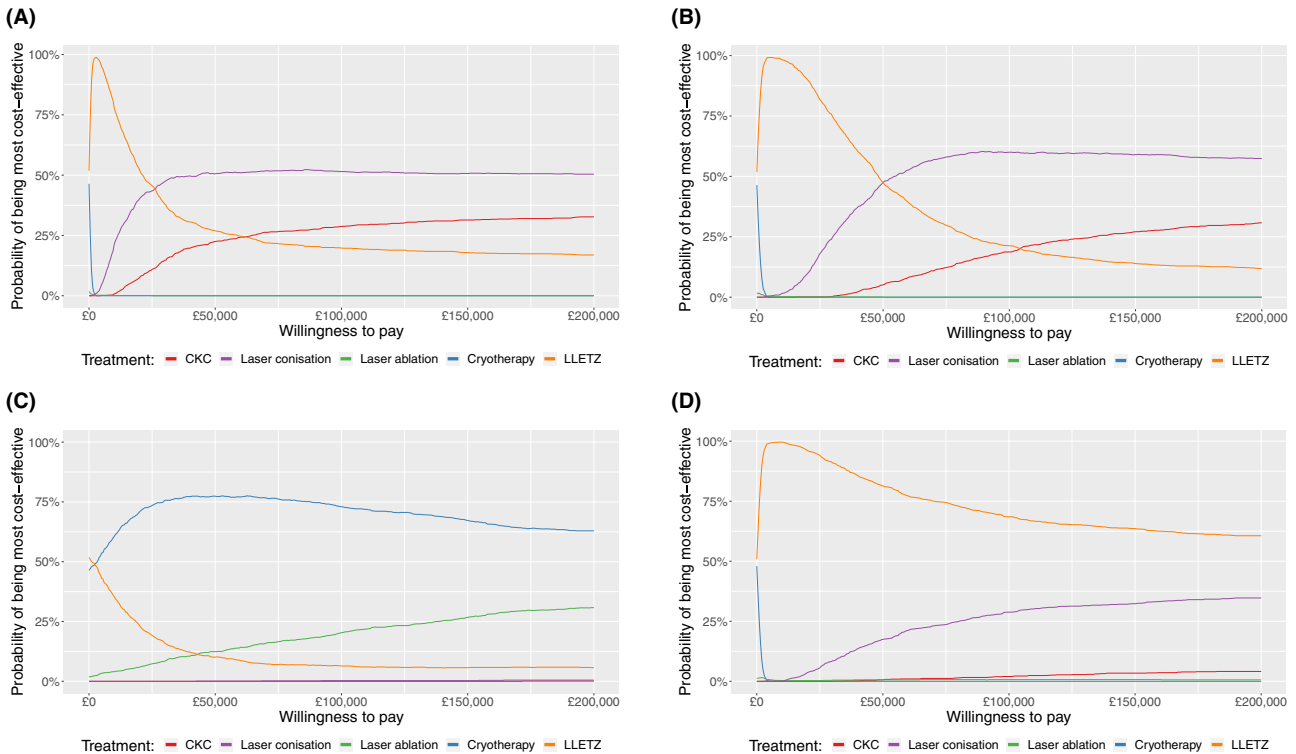
FIGURE 3 Cost-effectiveness acceptance curves for: (A) hrHPV+ at 6 months; (B) CIN2+ over the 10-year period; (C) preterm birth; and (D) CIN2+ in combination with preterm birth (on the assumption that each woman had, on average, 0.76 live births). CIN, cervical intraepithelial neoplasia; CKC, cold knife conisation; hrHPV, high-risk human papillomavirus; LLETZ, large loop excision of the transformation zone.
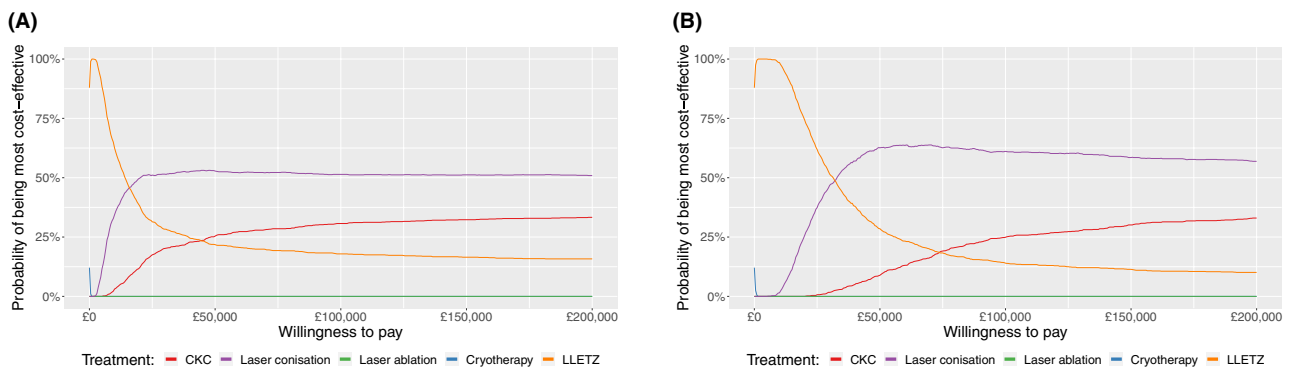

FIGURE 4 Cost-effectiveness acceptance curves for (A) at 6 months and (B) CIN2+ over the 10-year period (on the assumption that each woman had, on average, zero live births). CIN, cervical intraepithelial neoplasia; CKC, cold knife conisation; hrHPV, high-risk human papillomavirus; LLETZ, large loop excision of the transformation zone.

conisation was the most cost-effective treatment if the willingness to pay exceeded those thresholds (Figure 4). Cost-effectiveness planes are shown in Figure S6.

4 | DISCUSSION

4.1 | Main findings

This study compared different local treatment techniques for CIN in England and modelled their cost-effectiveness compared with 'usual care' (LLETZ). Our cost-effectiveness analyses highlighted the importance of considering both oncological and reproductive outcomes when comparing different excisional and ablative treatment techniques.

In the main analysis of young women, we demonstrated that LLETZ was the most cost-effective treatment for oncological outcomes (CIN2+) up to a willingness-to-pay threshold of £50,000; laser conisation would become the most cost-effective treatment only if the NHS was willing to invest more than £50,000 to avert one CIN2+ case, but this threshold is unaffordable for most health services. For reproductive outcomes, cryotherapy was the most cost-effective treatment at all thresholds. However, cryotherapy is associated with an unacceptably high risk of treatment failure[10]; thus, when reproductive outcomes (preterm

birth) were seen in the context of oncological outcomes (CIN2+), we found that LLETZ was the most cost-effective treatment at all thresholds. Owing to the high risk of treatment failure, British guidelines recommend against cryotherapy for the treatment of high-grade disease,[12] but cryotherapy is considered an acceptable treatment by the World Health Organization (WHO), especially in countries with limited resources.[25] Our cost-effectiveness analysis provides further evidence that cryotherapy should not be performed when other treatments are available.

In a separate analysis we assumed that our population only consisted of older women who have completed their childbearing. In this scenario, we found that LLETZ was the most cost-effective treatment for oncological outcomes (CIN2+) up to a threshold of £31,500, but that laser conisation would become the most cost-effective treatment if the NHS was willing to invest more than £31,500 to avert one CIN2+ case. Given that rates of unsatisfactory colposcopy and treatment failure are higher in older women than younger women,[10] the NHS could consider investing more money in this select group of women. Our results elucidate the additional NHS costs for treatments other than LLETZ, and can be used to support clinicians, when developing a more personalised management strategy for treatment, healthcare payers, when commissioning services within the NHS resources available, and health policymakers, when drafting treatment guidelines. Although we did not include NETZ in the cost-effectiveness analysis, owing to limited data in our NMA, it is expected that the outcomes for NETZ are likely to be similar to those for laser conisation.

4.2 | Strengths and limitations

This study has several strengths. To the best of our knowledge, this is the first economic study to compare the cost-effectiveness of different local treatment techniques for CIN. We compared the different interventions looking at a broad spectrum of oncological outcomes and complications (surgical or reproductive). We considered not only short-term economic impacts for the NHS (such as the cost of the first round of treatment and surgical complications, including bleeding and infection), but also long-term economic oncological consequences as well as hospital care costs that relate to preterm disabilities. The data used to build our main analysis was informed by expert input, after these experts had assessed the results of our NMA, the results of the best available studies and the audit data. Probabilistic sensitivity analyses took into account the uncertainty of expert input and tested the robustness of our model.

Our analyses are not without limitations. To source NHS unit costs, we relied on expert input when standardised unit costs were not available from national tariff schedules or from the literature. Owing to a lack of data, we did not consider 'quality-adjusted life years' (QALYs) as suggested by NICE when comparing the cost-effectiveness of different interventions.[21] This would have allowed us to compare treatments across all outcomes. Instead, we created a composite outcome that considered both CIN2+ rates and preterm birth rates (on the assumption that these two outcomes have equal clinical significance). This study considered the perspective of the NHS, looked at the impact of treatments and oncological and reproductive consequences on the NHS budget, and assumed that the costs of preterm birth consequences were driven by hospitalisation costs for early years.[15] Additional studies are needed to broaden the evaluation perspective to society and to account for the income loss for women diagnosed with cervical cancer, as well as for the impact of prematurity on special educational needs, social services, and on families and carers.[26,27]

4.3 | Interpretation

In our recently published NMA we concluded that LLETZ achieves the optimal balance between oncological and reproductive outcomes[10]; herein, we have complemented our NMA results and have shown that LLETZ is the most cost-effective CIN treatment for women of reproductive age. Although evidence from cost-effectiveness analyses is country specific and relies largely on local policies and tariffs, these findings are likely to be applicable to most high-income settings with similar health systems. Our decision-analytic modelling approach can serve as a blueprint for other settings to prioritise treatment decisions. This study contributes to a limited evidence base on the cost-effectiveness of alternative CIN treatments. We only found one cost-effectiveness analysis published over 20 years ago that compared four different treatment strategies for high-grade disease (CKC or cryotherapy, preceded by punch biopsies; LLETZ or cryotherapy, preceded by punch biopsies; LLETZ, preceded by punch biopsies; and LLETZ without prior punch biopsies). However, this study did not assess CKC and cryotherapy separately, and focused exclusively on the costs of oncological outcomes and surgical complications without considering the cost impact of reproductive outcomes.[28] A number of other cost-effectiveness analyses have assessed various comparisons but not the cost-effectiveness of treatment modalities, e.g. 'select and treat' after punch biopsies versus 'see and treat' without punch biopsies, using the same treatment technique,[29] different management strategies for low-grade disease, with immediate treatment versus surveillance,[30] or different cervical screening strategies (e.g. cytology-based screening vs hrHPV-based screening, with different screening intervals or different ages at onset of screening),[31–33] or have compared adjuvant colposcopy tools with colposcopy alone.[34] Of those cost-effectiveness analyses, only one considered the costs of reproductive morbidity.[33]

5 | CONCLUSION

Overall, LLETZ is the most cost-effective treatment for young women of reproductive age. For older postmenopausal

women, LLETZ remains a cost-effective treatment, but laser conisation (or other techniques with similar radicality) could also be considered if the willingness to pay to avoid one CIN2+ recurrence exceeds £31,500.

CONFLICT OF INTEREST STATEMENT
None declared.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT
None needed.

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REFERENCES
1. Kyrgiou M, Koliopoulos G, Martin-Hirsch P, Arbyn M, Prendiville W, Paraskevaidis E. Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis. Lancet. 2006;367(9509):489–98.
2. Arbyn M, Kyrgiou M, Simoens C, Raifu AO, Koliopoulos G, Martin-Hirsch P, et al. Perinatal mortality and other severe adverse pregnancy outcomes associated with treatment of cervical intraepithelial neoplasia: meta-analysis. BMJ. 2008;337:a1284.
3. Kyrgiou M, Mitra A, Arbyn M, Stasinou SM, Martin-Hirsch P, Bennett P, et al. Fertility and early pregnancy outcomes after treatment for cervical intraepithelial neoplasia: systematic review and meta-analysis. BMJ. 2014;349:g6192.
4. Kyrgiou M, Athanasiou A, Paraskevaidi M, Mitra A, Kalliala I, Martin-Hirsch P, et al. Adverse obstetric outcomes after local treatment for cervical preinvasive and early invasive disease according to cone depth: systematic review and meta-analysis. BMJ. 2016;354:i3633.
5. Castanon A, Landy R, Brocklehurst P, Evans H, Peebles D, Singh N, et al. Risk of preterm delivery with increasing depth of excision for cervical intraepithelial neoplasia in England: nested case-control study. BMJ. 2014;349:g6223.
6. Kyrgiou M, Valasoulis G, Stasinou SM, Founta C, Athanasiou A, Bennett P, et al. Proportion of cervical excision for cervical intraepithelial neoplasia as a predictor of pregnancy outcomes. Int J Gynaecol Obstet. 2015;128(2):141–7.
7. Strander B, Hallgren J, Sparen P. Effect of ageing on cervical or vaginal cancer in Swedish women previously treated for cervical intraepithelial neoplasia grade 3: population based cohort study of long term incidence and mortality. BMJ. 2014;348:f7361.
8. Arbyn M, Kyrgiou M, Gondry J, Petry KU, Paraskevaidis E. Long term outcomes for women treated for cervical precancer. BMJ. 2014;348:f7700.
9. Martin-Hirsch PP, Paraskevaidis E, Bryant A, Dickinson HO. Surgery for cervical intraepithelial neoplasia. Cochrane Database Syst Rev. 2013;2013(12):CD001318.
10. Athanasiou A, Veroniki AA, Efthimiou O, Kalliala I, Naci H, Bowden S, et al. Comparative effectiveness and risk of preterm birth of local treatments for cervical intraepithelial neoplasia and stage IA1 cervical cancer: a systematic review and network meta-analysis. Lancet Oncol. 2022;23(8):1097–108.
11. NHS Digital. Cervical screening programme: national statistics (England, 2020-2021). 2021 [cited 2022 Nov 22]. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/cervical-screening-annual/england--2020-2021
12. Public Health England. Cervical screening: programme and colposcopy management. 2023 [cited 2023 Mar 26]. Available from: https://www.gov.uk/government/publications/cervical-screening-programme-and-colposcopy-management
13. Gosling JP. Methods for eliciting expert opinion to inform health technology assessment. 2014 [cited 2022 Oct 25]. Available from: https://www.semanticscholar.org/paper/Methods-for-eliciting-expert-opinion-to-inform-Gosling/38eba762cdaf5d6dae2fee2063bf776d5facec5b
14. Curtis L, Burns A. Unit costs of health and social care. Kent: University of Kent; 2019.
15. Guest JF, Keating T, Gould D, Wigglesworth N. Modelling the costs and consequences of reducing healthcare-associated infections by improving hand hygiene in an average hospital in England. BMJ Open. 2019;9(10):e029971.
16. National Health Service. 2020/21 National tariff payment system. 2020 [cited 2022 Oct 25]. Available from: https://www.england.nhs.uk/wp-content/uploads/2021/02/20-21_National-Tariff-Payment-System.pdf
17. Petrou S. The economic consequences of preterm birth during the first 10 years of life. BJOG. 2005;112(Suppl 1):10–5.
18. Behrman RE, Butler AS, editors. Preterm birth: causes, consequences, and prevention. Washington: National Academies Press; 2007.
19. Kalliala I, Anttila A, Nieminen P, Halttunen M, Dyba T. Pregnancy incidence and outcome before and after cervical intraepithelial neoplasia: a retrospective cohort study. Cancer Med. 2014;3(6):1512–6.

20. York Health Economics Consortium. Incremental cost-effectiveness ratio (ICER). 2016 [cited 2022 Oct 25]. Available from: https://yhec.co.uk/glossary/incremental-cost-effectiveness-ratio-icer

21. National Institute for Health and Care Excellence. Developing NICE guidelines: incorporating economic evaluation. 2022 [cited 2022 Oct 25]. Available from: https://www.nice.org.uk/process/pmg20/chapter/incorporating-economic-evaluation

22. R Core Team. R: a language and environment for statistical computing. 2022 [cited 2022 Nov 30]. Available from: https://www.R-project.org

23. Incerti D, Jansen JP. hesim: health economic simulation modeling and decision analysis. 2021.https://arxiv.org/abs/2102.09437

24. Office for National Statistics. Births in England and Wales: 2021. 2022 [cited 2023 Feb 14]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/livebirths/bulletins/birthsummarytablesenglandandwales/2021

25. World Health Organisation. WHO guidelines for the use of thermal ablation for cervical pre-cancer lesions. 2019 [cited 2022 Apr 17]. Available from: https://apps.who.int/iris/bitstream/handle/10665/329299/9789241550598-eng.pdf

26. Petrou S, Yiu HH, Kwon J. Economic consequences of preterm birth: a systematic review of the recent literature (2009-2017). Arch Dis Child. 2019;104(5):456–65.

27. Ginsburg O, Bray F, Coleman MP, Vanderpuye V, Eniu A, Kotha SR, et al. The global burden of women's cancers: a grand challenge in global health. Lancet. 2017;389(10071):847–60.

28. Holschneider CH, Ghosh K, Montz FJ. See-and-treat in the management of high-grade squamous intraepithelial lesions of the cervix: a resource utilization analysis. Obstet Gynecol. 1999;94(3):377–85.

29. Fung HY, Cheung LP, Rogers MS, To KF. The treatment of cervical intra-epithelial neoplasia: when could we 'see and loop'. Eur J Obstet Gynecol Reprod Biol. 1997;72(2):199–204.

30. TOMBOLA Group. Options for managing low grade cervical abnormalities detected at screening: cost effectiveness study. BMJ. 2009;339:b2549.

31. Bains I, Choi YH, Soldan K, Jit M. Clinical impact and cost-effectiveness of primary cytology versus human papillomavirus testing for cervical cancer screening in England. Int J Gynecol Cancer. 2019;29(4):669–75.

32. Kitchener HC, Canfell K, Gilham C, Sargent A, Roberts C, Desai M, et al. The clinical effectiveness and cost-effectiveness of primary human papillomavirus cervical screening in England: extended follow-up of the ARTISTIC randomised trial cohort through three screening rounds. Health Technol Assess. 2014;18(23):1–196.

33. Kamphuis EI, Naber SK, Danhof NA, Habbema JDF, de Groot CJM, Mol BWJ. Effect of cervical cancer screening programs on preterm birth: a decision and cost-effectiveness analysis. Obstet Gynecol. 2017;130(6):1207–17.

34. Peron M, Llewellyn A, Moe-Byrne T, Walker S, Walton M, Harden M, et al. Adjunctive colposcopy technologies for assessing suspected cervical abnormalities: systematic reviews and economic evaluation. Health Technol Assess. 2018;22(54):1–260.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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