Adjunctive colposcopy technologies for examination of the uterine cervix – DySIS, LuViva Advanced Cervical Scan and Niris Imaging System: a systematic review and economic evaluation

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Executive summary

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Health Technology Assessment 2013; Vol. 17: No. 8
DOI: 10.3310/hta17080

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Executive summary

Background

Cervical cancer is the most common cancer in women aged <35 years in the UK. Women in England between the ages of 25 and 64 years are invited for regular cervical screening every 3–5 years under the NHS Cervical Screening Programme. Most screening is conducted using liquid-based cytology (LBC).

Women with an abnormal cytology result, or repeated inadequate or borderline results, are referred for colposcopy. Colposcopy is used to visualise the cervix; if any abnormal area is identified, a biopsy is taken and sent for histopathological analysis to assess for the presence of cervical intraepithelial neoplasia (CIN) or cancer. CIN is a term describing abnormal changes in the cells of the cervix, ranging from CIN1 to CIN3 (which is precancerous).

Three adjunctive colposcopy technologies for examination of the uterine cervix have been included in this assessment: Dynamic Spectral Imaging System (DySIS) (developed by DySIS Medical, Edinburgh, UK), the LuViva Advanced Cervical Scan (developed by Guided Therapeutics, Norcross, GA) and the Niris Imaging System (developed by Imalux Corporation, Cleveland, OH). DySIS is a colposcope that incorporates a digital image analysis system [dynamic spectral imaging (DSI)], whereas LuViva and Niris are probes with image analysis systems, which are designed to be used in conjunction with a standard colposcope.

Objective

To determine the clinical effectiveness and cost-effectiveness of adjunctive colposcopy technologies for examination of the uterine cervix for patients referred for colposcopy through the NHS Cervical Screening Programme; the technologies under consideration are DySIS, LuViva and Niris.

Methods

This report contains reference to confidential information provided as part of the NICE appraisal process. This information has been removed from the report and the results, discussions and conclusions of the report do not include the confidential information. These sections are clearly marked in the report.

Clinical effectiveness

A systematic review of the evidence on the clinical effectiveness of DySIS, LuViva and Niris, compared with conventional colposcopy, for examination of the uterine cervix in patients referred for colposcopy through the NHS Cervical Screening Programme was performed. Sixteen electronic databases (including MEDLINE and EMBASE) and two clinical trials registries were searched from January 2000 to September–October 2011.

Data were extracted on study and participant characteristics and outcomes. Where sufficient data were available, the following diagnostic accuracy statistics [with 95% confidence intervals (CIs)] were calculated: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR) and negative LR. Where data were missing from publications or other study reports, the authors were contacted.

The quality of the included studies was assessed using the QUADAS-2 quality assessment tool for diagnostic studies, along with additional review-specific questions. The included studies were

heterogeneous in terms of participant characteristics and the different comparator technologies used, therefore, meta-analysis was not appropriate; the studies were grouped according to the adjunctive technology used and a narrative synthesis was presented.

Cost-effectiveness

A systematic review was conducted to identify potentially relevant studies for inclusion in the assessment of cost-effectiveness of colposcopy and the colposcopy adjuncts (DySIS, LuViva and Niris). No economic evaluation studies were found which met the inclusion criteria. However, a number of studies were identified examining different points in the management pathway, which contained useful inputs for the modelling process, several of which were UK based. Following contact with the authors of these reports, we were able to gain access to a recent electronic model (Kim E-J. *Modelling the cost-effectiveness of human papillomavirus (HPV) testing for triage of women with low-grade abnormal cervical smears: a study within the TOMBOLA trial*. MSc thesis. Sheffield: The University of Sheffield; 2010) (referred to here as the Sheffield model), examining the cost-effectiveness of screening in the UK.

The model was developed to assess the cost-effectiveness of the three devices compared with colposcopy for examination of the uterine cervix for the detection of cancerous and precancerous cervical tissue in patients referred for colposcopy through the NHS Cervical Screening Programme. The model measured outcomes in terms of quality-adjusted life-years (QALYs) and costs are evaluated from the perspective of the NHS and Personal Social Services with a time horizon of 50 years. The model involved two stages: first, a decision tree to model the diagnostic and treatment pathways for patients referred to colposcopy from the NHS Cervical Screening Programme; and, second, a Markov model based on the Sheffield model, which simulates the natural history of patients and captures future cytological screening and referrals to colposcopy to estimate the outcomes of the initial diagnosis and treatment choices.

Cost-effectiveness was assessed using incremental cost-effectiveness ratios (ICERs). Results were presented for each reason for referral to colposcopy from the NHS Cervical Screening Programme, as well as for the whole population referred. Sensitivity analyses were undertaken to examine the impact of different assumptions and sources of uncertainty on results. Secondary analyses were also undertaken assuming a higher QALY decrement and cost associated with excision treatment biopsy, as these were shown to be of importance in the model. As a result of the weaknesses in the studies of Niris and LuViva, these devices were excluded from the main analysis, with only indicative analyses undertaken.

Results

Clinical effectiveness

The systematic review identified a limited evidence base for the three adjunctive colposcopy technologies: two studies of DySIS, one study of LuViva and three studies of Niris.

The two studies of DySIS were well reported; the most recent and most clinically relevant study found that the sensitivity of DySIS for identifying CIN2+ disease was statistically significantly higher than the sensitivity of conventional colposcopy, although specificity was significantly lower with DySIS. Taking both sensitivity and specificity into account, the overall diagnostic accuracy was similar to that of conventional colposcopy. The combination of DySIS (the DSI colour-coded map) and conventional colposcopy resulted in the highest result for sensitivity, although specificity was lowered further. Based on study quality assessment, these results are likely to be reliable.

Poor reporting of the remaining studies, along with a high risk of bias in certain areas and concerns about applicability, meant that the results for LuViva and Niris are likely to be unreliable and of limited clinical relevance.

Cost-effectiveness

In the base case, for most reasons for referral, colposcopy alone was dominated by DySIS or DySIS plus colposcopy (i.e. colposcopy alone had worse expected outcomes in terms of QALYs and was more costly than either of the DySIS arms). However, even in cases where colposcopy alone was not dominated by DySIS alone, DySIS alone was still cost-effective at accepted thresholds for cost-effectiveness, with ICERs of £593, £1545 or £1687 per QALY for the referral groups possible invasion, possible neoplasia or inadequate cytology, respectively. For all reasons for referral, DySIS alone was more costly and less effective than DySIS plus colposcopy (i.e. DySIS alone was dominated). Therefore, the base case indicates that DySIS plus colposcopy was cost-effective at accepted cost-effectiveness thresholds. These results were found to be robust by sensitivity analyses.

One feature of the model using base-case parameter values was that a higher specificity for a given management option resulted in worse outcomes and a higher ICER. This reflects the fact that the model suggests that treatment of CIN1 cases is more effective and cost-effective than watchful waiting with the base-case values for the cost and QALY decrement associated with an excision biopsy. This may suggest that these parameter values are too low. Separate secondary analyses were, therefore, undertaken in which the QALY decrement of treatment biopsy was increased (to 0.13 from 0.005 in the base case) or the cost of treatment biopsy was increased (to £2758 from £97 in the base case). Even with these values, DySIS alone and DySIS plus colposcopy appeared cost-effective for most of the reasons for referral and cost-effective for the overall (weighted) population.

Threshold analyses were also undertaken to find at what QALY decrement or cost of treatment biopsy DySIS alone or DySIS plus colposcopy would be considered not cost-effective for the total patient population at a threshold of £20,000 per QALY. It was established that the QALY decrement of treatment biopsy would have to be 0.38 (or 139 healthy days) for DySIS alone not to be cost-effective, or 0.42 (or 153 healthy days) for DySIS plus colposcopy not to be cost-effective, compared with colposcopy alone. The cost of treatment biopsy would have to increase to £7968 for DySIS alone or £8912 for DySIS plus colposcopy (compared with £97 in the base case) for either to appear not cost-effective compared with colposcopy alone at a cost-effectiveness threshold of £20,000 per QALY.

Two further analyses were undertaken comparing LuViva and Niris with DySIS plus colposcopy. As a result of the unreliability of the clinical evidence on the LuViva and Niris devices, these analyses are indicative only and should be interpreted with caution. Assuming the devices exhibit the same specificity of DySIS plus colposcopy, the sensitivity of LuViva would have to be 83% and the sensitivity of Niris 86% for either to be considered cost-effective compared with DySIS plus colposcopy at a threshold of £20,000 per QALY.

Conclusions

DySIS, particularly when combined with colposcopy, has higher sensitivity than conventional colposcopy alone. There is no reliable evidence on the clinical effectiveness of the other adjunctive colposcopy technologies, LuViva and Niris.

The results of the economic analysis suggest that DySIS plus colposcopy is less costly and more effective than both DySIS alone or colposcopy alone, and that these results are robust to the numerous sensitivity analyses that were undertaken. Given the lack of reliable evidence on LuViva and Niris, only indicative sensitivity analyses based on the costs of these devices were undertaken, which do not allow us to draw any conclusions regarding their potential cost-effectiveness.

There is some uncertainty about how generalisable these findings will be to the population of women referred for colposcopy in the future, owing to the introduction of the human papillomavirus (HPV) triage test and uptake of the HPV vaccine.

Implications for service provision

The introduction of any of these new devices may require additional staff training, which may result in additional upfront costs that were not considered in the analysis. These costs may be actual training costs paid to the manufacturer but might also be costs associated with the additional time or initial accuracy of staff as they learn to use the new device.

Suggested research priorities

In light of the risk of bias affecting the results of the studies of LuViva and Niris, further well-designed studies are needed to reliably evaluate their diagnostic accuracy. The bias risk was a result of the reference standard methodologies used, with further uncertainty about study reliability stemming from the unclear reporting in relation to other possible sources of bias.

Further research is needed to inform the appropriate management of CIN1 and assess the robustness of the current model findings regarding the cost-effectiveness of CIN1 treatment.

Future studies on the diagnostic accuracy of such technologies should provide results for each diagnostic category (clear, CIN1, CIN2, CIN3, possible invasion and possible neoplasia) rather than sensitivity and specificity at a single cut-off.

Study registration

This study is registered as PROSPERO Record CRD42011001614.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Publication

Wade R, Spackman E, Corbett M, Walker S, Light K, Naik R, *et al*. Adjunctive colposcopy technologies for examination of the uterine cervix – DySIS, LuViva Advanced Cervical Scan and Niris Imaging System: a systematic review and economic evaluation. *Health Technol Assess* 2013;**17**(8).

Health Technology Assessment

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Five-year impact factor: 5.596

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index and is assessed for inclusion in the Database of Abstracts of Reviews of Effects.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (http://www.publicationethics.org/).

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This report

The research reported in this issue of the journal was commissioned and funded by the HTA programme on behalf of NICE as project number 11/44/01. The protocol was agreed in September 2011. The assessment report began editorial review in February 2012 and was accepted for publication in July 2012. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health.

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