Adjunctive colposcopy technologies for assessing suspected cervical abnormalities: systematic reviews and economic evaluation

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Scientific summary

Technologies for assessing cervical abnormalities

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Background

Colposcopy is used to detect cervical intraepithelial neoplasia (CIN) and cervical cancer in women with abnormal results from a cervical smear test or with high-risk human papillomavirus (hrHPV) infection. Dynamic Spectral Imaging System (DySIS)map (DySIS Medical Ltd, Edinburgh, UK) and ZedScan (Zilico Limited, Manchester, UK) are two technologies that can be used as adjuncts to conventional colposcopy, which may improve the detection of CIN and cancer.

Women are referred to colposcopy from the cervical screening programme. This programme currently has two different algorithms for referral. In the human papillomavirus (HPV) triage algorithm, a cytology test (e.g. a Pap smear) is performed and, if positive, this is followed by a HPV test. In the HPV primary screening algorithm, the HPV test is performed first, and only if the test result is positive is a cytology test performed.

Objectives

To assess the clinical effectiveness and cost-effectiveness of adjunctive colposcopy technologies (DySISmap and ZedScan) for assessing suspected cervical abnormalities in people referred for colposcopy as part of the NHS Cervical Screening Programme (NHSCSP) under either the HPV triage screening algorithm (including test of cure) or the HPV primary screening algorithm (including test of cure).

Methods

Assessment of clinical effectiveness

Three systematic reviews were conducted. A range of bibliographic sources (including MEDLINE and EMBASE) were searched from inception to April 2017 for published and unpublished literature.

For the diagnostic accuracy outcomes, we included prospective cohort studies of DySISmap or ZedScan reporting data to calculate diagnostic accuracy estimates. For the clinical effectiveness outcomes, we included any study in which DySISmap or ZedScan was used that reported relevant clinical outcomes, such as adverse events. For the implementation outcomes, we considered all publications reporting issues related to the implementation of DySISmap or ZedScan.

For all reviews, the eligible population was patients who were referred to colposcopy through a cervical screening programme because of a suspected abnormality.

The index tests were DySISmap or ZedScan as an adjunct to colposcopy used for the diagnosis of CIN or cervical cancer. The reference standard was histopathology based on excisional or treatment biopsies.

Two researchers screened the titles and abstracts and all full-text papers subsequently obtained for assessment. Data extraction and quality assessment were performed by at least one researcher and checked by a second researcher. The risk of bias of diagnostic accuracy studies was assessed using a modified version of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 checklist.

For the diagnostic accuracy outcomes, bivariate models were fitted to calculate the summary estimates of sensitivity and specificity with 95% confidence intervals (CIs). Additional diagnostic accuracy results and results from the clinical effectiveness and implementation reviews were reported narratively.

Assessment of cost-effectiveness

Bibliographic databases were searched to identify cost-effectiveness evidence. Only full economic evaluations were considered. Study characteristics and design issues were extracted and critically appraised. The main findings of existing economic evaluations were summarised and important structural assumptions and areas of uncertainty were highlighted.

The review informed the de novo decision-analytic model. This 'York model' used a patient-level state-transition modelling approach to estimate the cost-effectiveness of DySISmap and ZedScan for people who are referred for colposcopy through the NHSCSP under either HPV triage or the HPV primary screening algorithm.

The model was populated using results from the systematic clinical effectiveness and cost-effectiveness reviews, routine sources of cost data, expert clinical opinion and data provided by the manufacturers and other investigators. A time horizon of 60 years (lifetime) was used and the costs and outcomes were discounted at a rate of 3.5%. A 2015–16 price year was used.

Analyses were run separately for each routine screening model (HPV triage protocol and HPV primary screening protocol), different types of clinic (see and treat, watchful waiting) and for different reasons for referral (all referrals, referrals for low-grade dyskaryosis and referrals for high-grade dyskaryosis). The incremental cost-effectiveness of DySISmap and ZedScan, compared with conventional colposcopy alone, was determined based on an assessment of long-term NHS and Personal Social Services costs and quality-adjusted life-years (QALYs). Sensitivity and scenario analyses were undertaken to explore the robustness of the results to changes in the parameter inputs, structural assumptions of the model and the time horizon.

Results

Diagnostic accuracy

Eleven studies were included in the diagnostic review: nine of DySIS and two of ZedScan. Only one study was rated as being at a low risk of bias overall; the remaining 10 studies were rated as being at a high risk of bias.

The sensitivity of adjunctive DySIS use was found to be higher (81.25%, 95% CI 72.2% to 87.9%) than that of standard colposcopy alone (57.91%, 95% CI 47.2% to 67.9%), but with lower specificity (70.40%, 95% CI 59.4% to 79.5%) than colposcopy (87.41%, 95% CI 81.7% to 91.5%).

Only two included studies investigated ZedScan, led by the same researchers in Sheffield. One was a study of the ZedScan and did not report the full diagnostic accuracy results for colposcopy alone. The other was a study of a precommercial ZedScan prototype. These issues significantly limited our ability to assess the diagnostic accuracy of ZedScan. (Confidential information has been removed.)

The specificity of all methods was strongly dependent on what reference standard was used in women with no colposcope-detected high-grade CIN. This means that the actual diagnostic accuracy of colposcopy and adjunctive colposcopy is uncertain.

Clinical effectiveness

Three studies (two of DySIS and one of ZedScan) were included and reported very limited data on adverse events.

Implementation

Five studies (four of DySIS and one of ZedScan) were included. There is some evidence that DySISmap as an adjunct to colposcopy is generally well received by patients referred for colposcopy and that adjunctive DySIS was perceived by clinicians to improve the accuracy of colposcopy and confidence in their diagnostic

decisions and biopsy site selection (two studies). There is evidence that the additional time required to use ZedScan is minimal in experienced colposcopists.

Cost-effectiveness

Two studies were included in the review of cost-effectiveness. One was an independent assessment of the cost-effectiveness of DySIS developed for the previous National Institute for Health and Care Excellence (NICE) DG4 assessment [NICE. *Adjunctive Colposcopy Technologies for Examination of the Uterine Cervix – DySIS and the Niris Imaging System*. Diagnostics guidance (DG4). NICE. 2012. URL: www.nice.org.uk/guidance/dg4 (accessed 10th January 2016).]. The other study was a company-funded assessment of a prototype version of ZedScan. Neither study fully informed the current decision problem, which includes the current HPV triage protocol (including test of cure) and also the proposed HPV primary screening protocol.

The main results of the base-case analysis from the York model under the HPV triage protocol are:

- Dynamic Spectral Imaging System routinely dominated colposcopy alone, regardless of the type of clinics or the reason for referral. The only exception was for high-grade referrals in a watchful-waiting clinic setting, in which DySIS was more costly and more effective, with an associated incremental cost-effectiveness ratio (ICER) of £675 per QALY.
- ZedScan also dominated colposcopy alone in see-and-treat clinics. However, in watchful-waiting clinics, ZedScan was always more effective than colposcopy alone, but was also more costly. The ICER for ZedScan in watchful-waiting clinics ranged from £272 (low-grade referrals) to £4070 per QALY (high-grade referrals).
- The indirect comparison between ZedScan and DySIS showed that ZedScan routinely appeared to be more effective but also more costly than DySIS. The ICER for ZedScan ranged from £109 per QALY for high-grade referrals in see-and-treat clinics to £9918 per QALY for high-grade referrals in watchful-waiting clinics.

The main results of the base-case analysis from the York model under the HPV primary screening protocol are:

- Dynamic Spectral Imaging System dominated colposcopy alone, except for high-grade referrals in watchful-waiting clinics in which the ICER was estimated to be £1095 per QALY.
- ZedScan dominated only colposcopy alone for high-grade referrals in a see-and-treat clinic. In all other cases, ZedScan was more effective but also more costly than colposcopy alone. The ICER ranged from £417 per QALY for low-grade referrals in see-and-treat clinics to £4922 per QALY for high-grade referrals in watchful-waiting clinics.
- ZedScan was always more effective but also more costly than DySIS. The ICER ranged from £426 per QALY for high-grade referrals in see-and-treat clinics to £8190 per QALY for high-grade referrals in watchful-waiting clinics.

The results appeared to be robust to a variety of sensitivity and scenario analyses.

There remains uncertainty regarding the cost-effectiveness of ZedScan given the challenges of comparing it with colposcopy. In the absence of a direct comparison between the alternative technologies, an indirect comparison was performed. However, these results should be considered to be exploratory in nature, given the lack of a robust direct comparison and the challenges identified more generally that arise from the limitations in the evidence base for ZedScan.

The cost-effectiveness results presented for the HPV primary screening protocols also require careful consideration. Our analysis is based on the current protocol and the assumption that the final HPV primary screening protocol may alter prior to HPV primary screening being rolled out nationally. Furthermore, key input data were derived from unpublished and preliminary results collected in the HPV pilot sites. Data collection is still ongoing and selection issues may limit the generalisability of the data used. Hence, the results under the HPV primary screening protocol should be considered to be exploratory and further analyses should ideally be undertaken when data collection has been completed and the implications of any selection effect are clearer.

Discussion

Extensive literature searches were conducted with an attempt to maximise the retrieval of potentially relevant studies. These included electronic searches of a variety of bibliographic databases, as well as the screening of clinical trial registers and conference proceedings to identify unpublished studies. The search strategy did not restrict by study design. The device manufacturers and study authors were contacted to provide additional data, and the review includes additional data from published studies and data from as-yet-unpublished studies. The review process followed recommended methods to minimise the potential for error and/or bias. The quality of the included studies was assessed and accounted for when interpreting the review results. Appropriate synthesis methods were employed by taking into account the heterogeneity of the study characteristics.

Only one study of the current version of ZedScan was available, limiting the ability to compare it with colposcopy. No studies directly compared DySIS and ZedScan. Very few data on participant subgroups were available. All but one study was rated as being at a risk of bias. In particular, there were few data on diagnostic accuracy in women with high-risk HPV.

There was very limited evidence relating to the clinical effectiveness of adjunctive DySIS or ZedScan, with little reporting of any potential adverse effects.

Conclusions

The use of adjunctive DySIS (DySISmap with DySIS video colposcope) increases sensitivity when compared with colposcopy alone, so it increases the number of high-grade CIN cases that are detected. However, it also reduces specificity when compared with colposcopy, so more women with no or low-grade CIN will be incorrectly judged as possibly having high-grade CIN. It might therefore increase unnecessary anxiety in women with an incorrect test result. It could lead to an increase in the number of unnecessary diagnostic biopsies (although evidence on whether or not this is actually the case is limited) and complications in subsequent pregnancies in women who did not require a biopsy.

The limited evidence precludes any definitive conclusions regarding the diagnostic accuracy of ZedScan, although it appears, like DySIS, to increase sensitivity and decrease specificity compared with colposcopy alone, when using the currently implemented ZedScan assessment algorithm. There is currently too little evidence to assess whether or not ZedScan is superior to DySIS.

The cost-effectiveness of both adjunctive technologies compared with standard colposcopy, under both the HPV triage and primary screening algorithms, appears to be favourable when compared against conventional thresholds used to determine value in the NHS. However, the limitations and uncertainties in the evidence base identified for ZedScan need to be carefully considered. The cost-effectiveness of both adjunctive technologies under the HPV primary screening protocol should also be reassessed when additional data become available from the pilot sites.

Given the limited number of studies of ZedScan, further and well-conducted diagnostic accuracy studies of ZedScan are needed, particularly to compare its diagnostic accuracy with that of standard colposcopy and in groups independent of the manufacturers. Diagnostic accuracy studies comparing DySIS and ZedScan directly may also be useful.

As most current studies have been in women referred to receive colposcopy on the basis of cytology screening, diagnostic accuracy studies in women referred from HPV primary screening (or specifically in women with hrHPV) are needed to assess whether or not the new screening programme will alter diagnostic accuracy.

Study registration

This review is registered on PROSPERO CRD42017054515.

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