MAVARIC – a comparison of automation-assisted and manual cervical screening: a randomised controlled trial

HC Kitchener,[1]* R Blanks,[2] H Cubie,[3] M Desai,[4] G Dunn,[5] R Legood,[6,7] A Gray,[7] Z Sadique[6] and S Moss,[2] on behalf of the MAVARIC Trial Study Group

[1]School of Cancer and Enabling Sciences, University of Manchester, St Mary's Hospital, Manchester, UK
[2]Cancer Screening Evaluation Unit, The Institute of Cancer Research, Sutton, UK
[3]Specialist Virology Centre, Royal Infirmary of Edinburgh, Edinburgh, UK
[4]Manchester Cytology Centre, Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK
[5]Health Sciences Research Group, School of Community Based Medicine, University of Manchester, Manchester, UK
[6]Health Services Research Unit, London School of Hygiene and Tropical Medicine, London, UK
[7]Health Economics Research Centre, University of Oxford, Oxford, UK

*Corresponding author

Executive summary

Health Technology Assessment 2011; Vol. 15: No. 3
DOI: 10.3310/hta15030

Health Technology Assessment
NIHR HTA programme
www.hta.ac.uk

Executive summary

Objectives

Cervical screening currently relies on manually read slides in which the cytoscreener scans the entire slide looking for abnormal cells. This study evaluated technology that assists reading cytology by automatically detecting abnormal fields of view on a slide and presenting these to a cytoscreener on an automated microscope. This could potentially achieve greater sensitivity and productivity, thus saving lives and achieving a more efficient use of the cytology workforce. This study had the following objectives:

- To determine the sensitivity of automation-assisted reading relative to manual reading.
- To determine any added productivity of automated reading.
- To estimate the comparative cost-effectiveness of automated and manual reading.
- To determine the reliability of 'no further review' (NFR) without any reading.

Design

Samples were randomised to a paired arm reported by both automated and manual reading and an arm with manual reading only. All of the cytology was liquid based, and the study incorporated randomisation of both widely used liquid-based cytology systems and their respective automated imaging technology; one of which ranks slides in terms of abnormality and will select around one-fifth as requiring NFR.

Setting

The samples were obtained from women undergoing cervical screening in the NHS programme, principally in general practices, in Greater Manchester, UK.

Samples

Samples from 73,266 women were obtained between March 2006 and February 2009; 72,837 were included in the study. Almost all of the women were aged 25–64 years (69,218). Randomisation resulted in 24,566 (33.7%) slides in the manual arm and 48,271 (66.3%) in the paired arm.

Intervention

In the paired arm, automation-assisted reading of slides was performed in addition to manual reading and management determined by the worse result. Low-grade cytological abnormalities were triaged by a human papillomavirus (HPV) test (Hybrid Capture 2®; Qiagen, Crawley, UK) to select women for colposcopy referral. All women with high-grade abnormalities were referred for colposcopy. If cervical intraepithelial neoplasia grade II (CIN2) or worse (CIN2+) was detected, the woman was treated. Additionally, a detailed economic analysis of the cytology reading was undertaken.

Main outcome measures

The primary outcome was the sensitivity of the final automated result relative to that of the final manual result in the paired arm. Secondary outcome measures included an assessment of productivity and estimates of cost-effectiveness, and an evaluation of the reliability of the NFR facility in the Becton Dickinson (BD) FocalPoint™ Guided Screener (GS) Imaging System (BD, Franklin Lakes, NJ, USA).

Results

The proportion of abnormal cytology management results by grade were: borderline, 3.6%; mild dyskaryosis, 2.4%; and moderate and severe dyskaryosis combined, 1.22%. These were very similar to England as a whole. The non-negative cytology amounted to 5.47% in the paired arm and 5.52% in the manual-only arm. Within the paired arm the proportion of discordant pairs on final result was 3.8% (1850/48,271); for 1.3% (625/48,271), the discordance was between inadequate and negative. Discordant pairs occurred in both directions with respect to manual and automated reading. There were 192 additional low-grade/HPV-positive abnormalities detected by manual reading only (manual positive/auto negative) and 47 additional high-grade abnormalities detected by manual reading only in the paired arm. The overall referral rate to colposcopy was 4.7%. The proportion with CIN2+ was 1.6% (398/24,566) and 1.5% (707/48,271) for the manual and paired arms respectively ($p = 0.10$). The primary outcome of the relative sensitivity for CIN2+ of automated reading compared with manual reading in the paired arm was 0.92 [95% confidence interval (CI) 0.85 to 0.95]. The relative specificity was 1.006 (95% CI 1.005 to 1.007).

Productivity in terms of the number of slides read per day by primary screeners was estimated to be 60%–80% higher for automated reading than for manual reading. The overall costs per case of CIN2+ detected were almost identical between automated and manual reading (£2892, 95% CI £2720 to £3098; and £2838, 95% CI £2676 to £3030 respectively). The overall costs per case of cervical intraepithelial neoplasia grade III (CIN3) or worse (CIN3+) detected are also very similar between automated and manual reading (£4762, 95% CI £4378 to £5245; and £4775, 95% CI £4400 to £5244 respectively). Manual screening is therefore slightly more expensive and effective, and could be considered cost-effective compared with automated reading if decision-makers were willing to pay at least £5000 each additional case of CIN2+ detected. NFR in the BD FocalPoint GS Imaging System was reported in 22% of slides and was a very reliable indicator of the absence of underlying disease, with only 3.1% of detected CIN2+ being missed by NFR, and even more so if NFR was restricted to routine screening slides. When both savings in staff time to read slides and the additional equipment costs were taken into account, utilising the NFR option generated cost savings. Based on all slides included in the MAVARIC (Manual Assessment Versus Automated Reading In Cytology) study, assessment of the incremental cost per case detected revealed that decision-makers would need to be willing to pay £2500 per additional case of CIN2+ detected for it to be more cost-effective to read slides manually instead.

Results of the lifetime modelling indicated that when life-years were used as an outcome measure, manual reading was within the £20,000–30,000 per life-year saved range in which the National Institute for Health and Clinical Excellence would neither accept nor reject this technology on cost-effectiveness grounds alone. Modelled results were also estimated for quality-adjusted life-years gained, but these are highly uncertain given the absence of trial evidence on utility values.

Conclusions

The principal finding was that automation-assisted reading was 8% less sensitive than manual in the detection of CIN2+ and 5% less sensitive for CIN3+. To a large extent, this was due to automation-assisted reading failing to detect cases of low-grade abnormalities that were detected in manual reading. The majority of missed cases were due to failure to detect abnormalities presented rather than location-guided errors. Despite the undoubted productivity gains that could be achieved in terms of slide throughput, there do not appear to be sufficient grounds to recommend automation. The slight gain in specificity is not of clinical importance; the positive predictive value (CIN2+) of additional manually read abnormal cytology leading to colposcopy referral would be in line with that of HPV-positive/mild abnormalities currently triaged to colposcopy. Secondly, given the pricing obtained from the companies and used in this study, the cost-effectiveness of automation-assisted reading is marginal at best, compared with manual reading. Thirdly, there was a general view among the cytoscreeners that they find the automation-assisted reading more monotonous and prefer manual reading.

Although automation-assisted reading did not compare favourably with manual reading, the robust evaluation of the NFR mode of the BD FocalPoint GS Imaging System showed it to be very reliable and able to achieve cost savings in staff time, even if some methods of manual rapid review were maintained for quality control purposes. A significant reduction in the number of slides needing full screening would enhance efficiency and turnaround times.

Were, however, conclusive evidence to emerge in the future that the sensitivity concerns had been resolved and the cost-effectiveness of automation significantly improved, then the recommendation against automation would warrant reconsideration.

Trial registration

This trial is registered as ISRCTN66377374.

Funding

The National Institute for Health Research Health Technology Assessment programme.

Publication

Kitchener HC, Blanks R, Cubie H, Desai M, Dunn G, Legood R, *et al*. MAVARIC – a comparison of automation-assisted and manual cervical screening: a randomised controlled trial. *Health Technol Assess* 2011;**15**(3).

How to obtain copies of this and other HTA programme reports

An electronic version of this title, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (www.hta.ac.uk). A fully searchable DVD is also available (see below).

Printed copies of HTA journal series issues cost £20 each (post and packing free in the UK) to both public **and** private sector purchasers from our despatch agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per issue and for the rest of the world £3 per issue.

How to order:

– fax (with **credit card details**)
– post (with **credit card details** or **cheque**)
– phone during office hours (**credit card** only).

Additionally the HTA website allows you to either print out your order or download a blank order form.

Contact details are as follows:

Synergie UK (HTA Department)
Digital House, The Loddon Centre
Wade Road
Basingstoke
Hants RG24 8QW

Email: orders@hta.ac.uk

Tel: 0845 812 4000 – ask for 'HTA Payment Services' (out-of-hours answer-phone service)

Fax: 0845 812 4001 – put 'HTA Order' on the fax header

Payment methods

Paying by cheque
If you pay by cheque, the cheque must be in **pounds sterling**, made payable to *University of Southampton* and drawn on a bank with a UK address.

Paying by credit card
You can order using your credit card by phone, fax or post.

Subscriptions

NHS libraries can subscribe free of charge. Public libraries can subscribe at a reduced cost of £100 for each volume (normally comprising 40–50 titles). The commercial subscription rate is £400 per volume (addresses within the UK) and £600 per volume (addresses outside the UK). Please see our website for details. Subscriptions can be purchased only for the current or forthcoming volume.

How do I get a copy of *HTA on DVD*?

Please use the form on the HTA website (www.hta.ac.uk/htacd/index.shtml). *HTA on DVD* is currently free of charge worldwide.

The website also provides information about the HTA programme and lists the membership of the various committees.

NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA programme is needs led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

Second, the HTA programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer reviewed by a number of independent expert referees before publication in the widely read journal series *Health Technology Assessment*.

Criteria for inclusion in the HTA journal series

Reports are published in the HTA journal series if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the journal was commissioned by the HTA programme as project number 03/04/02. The contractual start date was in August 2005. The draft report began editorial review in February 2010 and was accepted for publication in June 2010. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. 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 referees 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.

The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

ISSN 1366-5278

Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NETSCC, HTA.
Printed on acid-free paper in the UK by the Charlesworth Group.