Cancer diagnostic tools to aid decision-making in primary care: mixed-methods systematic reviews and cost-effectiveness analysis

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Declared competing interests of authors: William Hamilton has overseen the development of a suite of cancer risk assessment tools encompassing all the major adult cancers. Richard Neal has also contributed to some of these studies. The risk assessment tools are available at no cost to the NHS. William Hamilton is the chief investigator of the Electronic Risk Assessment Tools for Cancer (ERICA) trial, a philanthropically funded cluster randomised controlled trial of electronic risk assessment tools in primary care. As a result of this interest, William Hamilton excluded himself from the data analysis, although he contributed to the rest of the work, including writing the outputs. Anne E Spencer and Antonieta Medina-Lara also report supporting the ERICA trial. William Hamilton, Antonieta Medina-Lara and Anne E Spencer report grants from Gillings Foundation and minor support from Cancer Research UK for the ERICA trial. Antonieta Medina-Lara reports grants from the National Institute for Health Research during the conduct of the study and outside the submitted work.

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Scientific summary

Background

Tools based on diagnostic prediction models are available to help general practitioners diagnose cancer. It is unclear whether or not they lead to increased or quicker diagnoses, and whether or not they ultimately affect patient quality of life and/or survival.

Objectives

The objectives were to evaluate the evidence on the validation, clinical effectiveness, cost-effectiveness (by two different systematic reviews), and availability and use of cancer diagnostic tools in primary care.

Systematic review 1

Methods

Two systematic reviews were conducted to examine the clinical effectiveness (systematic review 1) and development, validation and accuracy (systematic review 2) of diagnostic prediction models for use by general practitioners to aid cancer diagnosis. The following electronic databases were searched in May 2017 and updated in November 2018: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, the Cochrane Library and Web of Science™ (Clarivate Analytics, Philadelphia, PA, USA). Titles, abstracts and full texts were screened independently by two reviewers.

Studies of any design were included in systematic review 1 if they assessed the clinical effectiveness of diagnostic tools in aiding decision-making among general practitioners for symptomatic patients presenting with features potentially indicative of cancer. An expanded definition of diagnostic tools was used, which included tools based on scoring systems/algorithms, as well as those based on prediction models.

Data extraction and assessment of risk of bias were completed by one reviewer and checked by a second reviewer. Owing to heterogeneity in tools, cancer sites, the outcomes measured and study design, a narrative review of the studies was conducted.

Results

Five studies met the inclusion criteria, and, between them, assessed three diagnostic tools: the risk assessment tools (as part of an education resource card in an Australian randomised controlled trial for lung, colorectal and prostate cancer, and mouse mats and desktop flip charts about colorectal and lung cancer in a UK-based pre–post study), a skin cancer algorithm (in a randomised controlled trial and a field trial, both based in Australia), and an online skin cancer recognition toolkit (in a UK-based case–control study).

Although the field trial and pre–post study reported a positive impact of the tools on outcomes, the results of the randomised controlled trials and the case–control study found no evidence that use of the tools was associated with better outcomes.

There is currently very little good-quality evidence to suggest that these tools can help improve general practitioner decision-making.
Systematic review 2

Methods
The search strategy was the same as that for systematic review 1. Studies of any design were included if they contained details on the development, validation or accuracy of diagnostic prediction models. Data extraction and assessment of risk of bias were completed by one reviewer and checked by a second reviewer. Owing to the heterogeneity of the tools, the cancer sites, the outcomes measured and the study design, a narrative review of the studies was conducted.

Results
A total of 43 studies met the inclusion criteria, including two systematic reviews. The searches identified evidence on 11 different prediction models in total, including risk assessment tools for 15 different cancer sites and QCancer® (ClinRisk Ltd, Leeds, UK) for six cancer sites, plus male and female versions for multiple cancers. Prediction models exist for 14 cancer sites, including models for multiple cancers. Colorectal cancer was associated with the greatest number of models (n = 6).

The majority of QCancer models, one risk assessment tool and five other models have been externally validated.

There are clear gaps in the evidence for further validation of existing models that have the potential to be implemented in primary care to aid general practitioner decision-making.

Updated review

Methods
A review was conducted to update the findings of a previous systematic review that examined the association between different durations of time from first symptom to diagnosis or treatment, and clinical outcomes, across all major cancers. The updated review was conducted to inform the decision-analytic model and its structural assumptions. It therefore includes a more focused review of colorectal cancer.

Results
The updated review identified 35 new studies, the overall findings of which were summarised in a table outlining whether each study reported a ‘positive association’ (i.e. statistically significant more favourable patient outcomes), a ‘negative association’ (i.e. statistically significant less favourable outcomes) or ‘no association’ (i.e. the findings were not statistically significant).

A more in-depth evaluation was conducted of colorectal cancer, which focused on studies identified during the updated review (n = 10) and better-quality studies identified in the previous review (n = 4). No meta-analyses were undertaken because of heterogeneity, which included variability in the intervals.

The majority of the colorectal cancer studies found ‘no association’ between various intervals and patient outcomes. A small number of studies (n = 4, but three used the same, or an overlapping, population) reported a positive association between shorter intervals and patient outcomes, but, paradoxically, a small number of studies (n = 3) also found a negative association.

These overall findings may reflect the U-shaped relationship between diagnostic interval and patient outcomes that was identified by some of the included studies, showing that both very short and long intervals were associated with poor outcomes. The review also identified important biases and other factors that may affect the findings of studies in this field.
Data for informing the economic decision model

Methods
The search strategy was designed to retrieve economic decision models for diagnosing or screening colorectal cancer. Colorectal cancer was the chosen focus for the economic analysis because its disease history in the UK setting has been researched in recent years. The methodological quality of the studies included was assessed in detail by two reviewers following the checklist for model studies by Philips et al. (Philips Z, Bojke L, Sculpher M, Claxton K, Golder S. Good practice guidelines for decision-analytic modelling in health technology assessment: a review and consolidation of quality assessment. *PharmacoEconomics* 2006;24:355–71). Data extraction and assessment of risk of bias were completed by one reviewer and checked by a second reviewer. A narrative review of the studies was conducted.

Results
The searches identified 18 studies that met the inclusion criteria, which were then included in the review.

Our review found no evidence on the cost-effectiveness of diagnostic tools for managing patients in primary care with suspected colorectal cancer, but identified one study of faecal immunochemical tests in the low-risk population of interest that modelled the diagnostic phase. Our critique of the model identified shortcomings in the way time to referral and mortality were analysed in the diagnostic phase, which were to be addressed in the de novo model developed in the present study.

Economic decision model

Methods
A simple analytical model of diagnostic pathway was used to illustrate the uncertainty inherent in the current evidence base, and to ask questions about the probable impact of the diagnostic tools, given the current evidence base.

The model takes as its starting point symptomatic patients presenting to primary care who undergo an initial clinical assessment. This model is then combined with an adaptation of an existing disease model from a published colorectal cancer screening study and used to identify the parameters contributing most to the overall decision uncertainty about the cost-effectiveness of decision tools, and where additional research might be targeted in the future. In the absence of evidence on the impact of the tools on the time to diagnosis, a structural assumption was used to link the sensitivity of diagnostic strategies with the expected duration of the referral interval. The mechanism of effect of all the strategies considered in the model is, therefore, a reduction in the time to diagnosis, made possible by a reduction in the referral interval.

Results
The analysis using the limited available data on current practice in the UK suggests that the survival benefit of faster referrals for cancer patients is higher than the risks associated with exposing the overwhelming majority of patients without cancer to colonoscopy. Given the uncertainty in the evidence base, it is unclear if the overall benefits are worth the additional health-care costs associated with those referrals.

The sensitivity and threshold analysis revealed that the cost-effectiveness results were particularly sensitive to uncertainty around the diagnostic accuracy of current standard practice and the specificity of the tools. Other areas of uncertainty highlighted by the model include the clinical effectiveness of the tools, the prevalence of cancer in the low-risk population for which these tools are intended, the cost of colonoscopy and the definition of current practice.
General practice survey

Methods
A cross-sectional postal survey was carried out to determine (1) the proportions of UK general practices and UK general practitioners with access to cancer decision support tools and (2) the proportion of general practices that use cancer decision support tools. Data collection occurred in July and August 2017. Questionnaires were posted to 4600 general practitioners in 975 randomly selected UK practices. Using data from general practices in England only, ordinary least squares regression subanalyses explored the association between access to cancer decision support tools and practice-level cancer diagnostic indicators published by Public Health England. Ethics approval was granted by the University of Exeter.

Results
Responses were received from 473 general practitioners and three registrars in 227 practices, giving response rates of 23.3% (practice level) and 10.3% (practitioner level). Responding practices had a median of 6 (interquartile range 4–8) general practitioners, of whom a median of 2 (interquartile range 1–3) responded to the survey. EMIS Web (EMIS Health, Leeds, UK) was the most frequently used software (96/227, 42.3%), followed by TPP SystmOne (The Phoenix Partnership, Leeds, UK) (74/227, 32.6%) and then INPS Vision (In Practice Systems Ltd, London, UK) (74/227, 32.6%) and then INPS Vision (In Practice Systems Ltd, London, UK) (32/227, 14.1%).

A total of 112 of the 476 general practitioners (23.5%, 95% confidence interval 19.7% to 27.6%) had access to a cancer decision support tool in either paper or electronic format, or both. At the practice level, at least one general practitioner in 83 of the 227 practices (36.6%, 95% confidence interval 30.3% to 43.1%) had access to a tool. Tools were available and likely to be used in 38 of the 227 practices (16.7%, 95% confidence interval 12.1% to 22.2%).

There was no difference in the mean 2-week-wait referral rate between practices that do and practices that do not have access to either type of tool, after adjusting for Index of Multiple Deprivation (mean difference 1.8 referrals per 100,000, 95% confidence interval –6.7 to 10.3). Access to either type of tool was not associated with a change in the proportion of 2-week-wait referrals that resulted in a diagnosis of cancer, after adjusting for the Index of Multiple Deprivation (mean difference –0.2, 95% confidence interval –1.0 to 0.6).

Discussion
Cancer decision support tools are available to general practitioners in approximately one-third of UK general practices, but are likely to be used in only one-sixth of practices.

Improvements in training and increasing familiarisation with the tool may increase the levels of uptake of these tools by UK general practices and general practitioners.

More research is needed to determine the comparative accuracy of the tools in studies that directly compare them with current standard practice and in the same low-risk suspected symptomatic patient population in primary care. To inform decisions about the use of the tools to aid diagnosis in primary care, such studies should aim to measure the impact of the tools on diagnostic intervals and, ideally, on clinical outcomes.

Conclusions
Our survey indicates that cancer decision support tools are currently not widely used in the UK. This may reflect our findings in systematic reviews 1 and 2 that there is limited evidence that these tools have a positive impact on patient outcomes.
As levels of uptake are currently low, it is possible to carry out a randomised controlled trial to assess whether or not these tools are genuinely helpful in improving the selection of patients for investigation for suspected cancer.

**Study registration**

This study is registered as PROSPERO CRD42017068373 and CRD42017068375.

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This report

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