Accuracy of blood-based biomarkers for screening precancerous colorectal lesions: a protocol for systematic review and meta-analysis

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ABSTRACT

Introduction Colorectal cancer (CRC) is the third most diagnosed cancer and the second most common cause of cancer mortality worldwide. Most CRCs develop through either the adenoma-to-carcinoma or the serrated pathways, and, therefore, detection and removal of these precursor lesions can prevent the development of cancer. Current screening programmes can aid in the detection of CRC and adenomas; however, participation rates are suboptimal. Blood-based biomarkers may help to address these low participation rates in screening programmes. Although blood-based biomarker tests show promise for cancer detection, limited attention has been placed on the sensitivity and specificity for detection of the precursor lesions. The aim of this research is to conduct a systematic review and meta-analysis to evaluate the accuracy of blood-based biomarker tests in detecting advanced precancerous lesions.

Methods and analysis This protocol was informed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses-Protocols (PRISMA-P) and results will be reported in line with the PRISMA guidelines. Literature searches will be conducted on PubMed, Embase and Web of Science. Two reviewers will conduct the searches, and independently screen them, according to title and abstract and then the full-text versions of those selected articles as well as the risk of bias via the Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2) tool. The Grading of Recommendations Assessment, Development and Evaluation guidelines will be used to validate the certainty of evidence for recommendations based on the risk of bias findings. Meta-analysis will be conducted where appropriate on groups of studies with low heterogeneity.

Ethics and dissemination No patient data will be included in our review and, therefore, ethics approval is not required. It is anticipated that the review will identify the most promising candidate biomarkers for clinical translation in the screening of advanced precancerous lesions. The results will be published in a peer-reviewed journal.

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INTRODUCTION

Colorectal cancer (CRC) is the third most diagnosed cancer and the second most common cause of cancer mortality worldwide.1 In Australia, the age-standardised CRC incidence rate is approximately 50 per 100 000 people.2 CRC screening programmes (colonoscopy and/or faecal-based screening measures) have demonstrated efficacy in reducing both CRC incidence and mortality.3 4 CRC develops through the adenoma (or sessile serrated) carcinoma pathway, where precancerous lesions such as advanced adenomas and sessile serrated lesions may progress to CRC.5 6 The purpose of screening is to detect CRC at an early stage, enabling earlier interventions, which can lead to more efficacious treatment options and better patient outcomes, including reduced morbidity and mortality. Furthermore, screening can also assist in the detection of precancerous lesions, such as adenomas and advanced sessile serrated lesions that can be removed at colonoscopy, preventing approximately 80% of cancers.7 8 While colonoscopy is used as the main form of screening in several countries,9 there are risks associated with the procedure such as bowel perforations (3.1/10 000 procedures) and major bleeding (14.6/10 000).10 Colonoscopy can also be expensive, and many countries have limited capacity and resources for this procedure.
Therefore, implementation of less-invasive strategies for screening for precancerous lesions is needed.

The faecal occult blood test, in particular, the one using faecal immunochemical test (FIT) technology, which detects the level of human haemoglobin in the stool, has been shown to have benefit in the early detection and prevention of CRC.\(^\text{10-12}\) Most organised CRC screening programs around the world use FIT, mainly focusing on people at average risk (ie, no family history\(^\text{13}\) and/or no previous precancerous lesions).\(^\text{14-16}\) As outlined in a recent review,\(^\text{16}\) FIT appears to maintain both high sensitivity (range 55%-100%) and specificity (range 77%-97%) across 12 previous studies in the detection of CRC.\(^\text{15,17}\) While FIT has high accuracy for CRC detection, it can only detect up to 40% of advanced adenomas\(^\text{14}\) and only 16% of advanced sessile serrated lesions\(^\text{18}\) (depending on the positivity threshold applied and the number of samples collected). Even though FIT has good sensitivity for detecting CRC, the participation rate in FIT CRC screening programs is low, mainly due to faecal aversion and other issues, leading to low acceptability in consumers.\(^\text{19}\) An earlier study reported 78% of those surveyed preferring blood-based tests over faecal tests.\(^\text{19}\) Furthermore, 83% of consumers would also prefer to have blood-based tests over colonoscopy, indicating the high acceptance rates of blood sampling over current screening options.\(^\text{20}\) This highlights the need for blood-based biomarkers, which may improve participation in CRC screening as well as potentially increasing sensitivity for detection of precancerous colonic lesions.

Blood-based biomarker tests can target the various changes occurring along the advanced adenoma to carcinoma pathway, contributing to aberrant protein, metabolic and immune functions.\(^\text{6,21}\) Following these early initiating events, hyperproliferation of the colorectal epithelial cells can lead to the formation of polyps, which if left in place, can become adenomas and ultimately become invasive cancer. An alternate pathway (proposed more recently) is that of the alternative serrated pathway (15%-30% of CRC),\(^\text{22}\) where the precursor lesion is the sessile serrated lesion. A useful diagnostic blood biomarker should be sensitive and specific for detecting early neoplastic transformation as well as for CRC and have clinical accuracy to allow for optimal detection of CRC and precancerous lesions.\(^\text{15,17}\) To date, there are no reviews investigating the accuracy of blood-based biomarkers for detection of advanced colonic adenomas and/or sessile serrated lesions. This project aims to investigate the sensitivity and specificity of blood-based biomarkers for the detection of advanced colonic adenomas and advanced sessile serrated lesions.

Objectives

1. To evaluate the accuracy (sensitivity and specificity) of blood-based biomarkers for detection of important precancerous lesions, namely, advanced colorectal adenomas and advanced sessile serrated lesions.

2. To determine whether the accuracy of blood-based biomarkers is influenced by clinicopathological features of precancerous lesions.

METHODS AND ANALYSIS

The protocol for this review was based on Cochrane guidelines,\(^\text{23-24}\) Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines\(^\text{25-26}\) and other reviews already conducted in this area.\(^\text{23-26}\) Registration was registered with PROSPERO (International Prospective Register of Systematic Reviews), an international database for systematic reviews prospectively registered by the Centre for Reviews and Dissemination of the University of York (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD420211285173). This study commenced on October 2021 and is anticipated to be ready for publication in May 2022.

Patient and public involvement

The development of the research question and outcomes measures has been informed by patients’ priorities, experience and preferences through regular contact with consumer groups, including Cancer Voices Australia. These consumers had previous experience either as a patient or support person for someone with CRC or had experience with having adenomas detected at colonoscopy. Provision for ‘ad hoc’ comments on the research process will also be facilitated due to regular contact with these groups. Patients will not be involved in the analysis and data collection of the systematic review and meta-analysis.

Eligibility criteria

Population

People over the age of 18 of either sex with a diagnosis of advanced adenomas and/or sessile serrated lesions based on colonoscopy findings, who have also had any blood-based biomarker test, will be included in the study. Advanced adenoma features are defined as advanced are polyp size ≥10 mm, villous features or high-grade dysplasia,\(^\text{30-32}\) whereas advanced sessile serrated lesions include those with dysplastic changes and/or size ≥10 mm\(^3\). These definitions for advanced precancerous lesions match Australian\(^\text{34}\) and US\(^\text{35}\) guidelines. Studies investigating high-risk patients (eg, familial risk and hereditary syndromes) will be excluded as this does not represent the average population risk for development of colorectal adenomas or sessile serrated lesions. Furthermore, only studies published after 2006 will be included given the increase in the number of studies from this period and the changes in technology to accurately detect blood-based biomarkers.

Intervention

This review will consider studies that evaluate diagnostic accuracy (sensitivity and specificity) of blood-based biomarkers for detection of advanced adenomas and/or advanced sessile serrated lesions. The blood biomarker
The main outcomes to be evaluated are:

1. CRC, colorectal cancer.
2. Of colonic neoplastic disease and/or (2) individuals with precancerous lesions alongside (1) individuals with no evidence of colonic neoplastic disease and/or (2) individuals with CRC.

Outcomes
The main outcomes to be evaluated are:

1. Accuracy: the sensitivity and specificity of a blood-based biomarker test to detect advanced precancerous lesions.
2. How the accuracy of the test to detect advanced adenomas/sessile serrated lesions compared to its ability to detect CRC.

Secondary outcomes of interest are:
1. Whether there have been investigations into the cause of false-positive blood test results in participants without adenomas, serrated lesions or CRC.
2. Whether the blood test can detect adenomas/sessile serrated lesions in certain places of the colon (eg, distal vs proximal).
3. The association between the blood test results and pathology of the precancerous lesions.

Measures of effect: sensitivity will be presented on a 0 (least sensitive) to 1 (most sensitive) scale on Forest plots produced from the analysis. Concurrent analysis of sensitivity/specificity will be presented on a receiver operating characteristic (ROC)/area under the curve (AUC) for the combination of all the tests.

Studies
Given initial searches so far, it is anticipated that the level of evidence for this review is most likely to be based on observational (and some experimental studies), including cohort, case–control and cross-sectional designs. The inclusion and exclusion criteria for this review are summarised in table 1.

Information sources
Information sources will be restricted to publications in English and articles published after 2006. Specific search strategies using medical subjective heading (MESH) will be used where appropriate. The following databases will be used for the literature search: PubMed, Embase (OVID interface) and Web of Science. Authors who have published conference abstracts of work not yet published in peer-reviewed journals as a full-text original research article will be contacted to identify relevant unpublished literature. Grey literature will be included in the review via a Google Scholar search. White papers and industry databases were deemed outside the scope of the review.

Search strategy
The search will be conducted by two authors (RG and TJHL) and informed by subject-specific expertise (ELS, JMW, MMW, GPy). The keyword search strategy was developed for PubMed and identified appropriate MESH keywords to ensure completeness of the search. If MESH search terms do not add any further hits, these will be removed and only keywords used to improve the precision of the search approach. Different search terms may be used to reflect differences across the three databases.

| Table 1 | Summary of inclusion and exclusion criteria |
|---------|--------------------------------------------|
| **Inclusion criteria** | |
| Population | Adult patients of both sexes with a diagnosis of colonic advanced adenomas and/or advanced sessile serrated lesions based on colonoscopy outcomes as a part of screening, diagnostic or surveillance, and who have also had blood collected prior to polypectomy for biomarker analysis. |
| Intervention/exposure | Blood-based biomarker methodology is explained in detail, including the nature of the biomarker (eg, DNA, miRNA), quantitation technique, preparation method, accuracy for patients with colonic adenomas/sessile serrated lesions. |
| Comparison | Blood-based biomarker studies in non-cancer controls and/or those with colorectal cancers. |
| Study type | Quantitative observational and experimental studies. |

| **Exclusion criteria** | |
| Population | Those without a diagnosis of advanced colonic adenomas/sessile serrated lesions based on colonoscopy (ie, otherwise healthy controls or those with CRC). Those where colonoscopy has been completed for familial risk conditions. |
| Intervention/exposure | Non blood-based biomarkers (eg, faecal biomarkers). |
| Study type | Studies not in English, published prior to 2006, review articles, articles investigating blood-based biomarkers with in-vitro or animal models. Those not including a measure of test sensitivity. |

CRC, colorectal cancer.
The initial PubMed search strategy is included in the online supplemental table 1.

Two authors (RG and TJHL) under the guidance of the other authors (ELS, JMW, MMW, GPY) will search all information sources to identify suitable studies and then independently screen the full-text articles of all eligible studies. Information extracted (using a specified extraction template) will be completed by RG, with accuracy checked by TJHL. There will be no blinding by author, research group and/or institution in the included studies.

**Data management**

The complete record for each eligible study (including citation, abstract and other identifiable information) will be imported into Endnote V.20 (Clarivate Analytics). The full-text version for all included studies will be obtained and store in Endnote V.20. Screening will be carried out using a predetermined template to reflect the above stated inclusion and exclusion criteria.

**Selection process**

The study selection process aims to reflect the best practice guidelines outlined in the Cochrane handbook.23 Initial screening aims to only include studies aligning with the inclusion criteria readily identifiable from the title and abstract. The reason for exclusion for each study will be recorded. Where eligibility is unclear, the reviewers will obtain and review the full text of the article, using the predetermined screening template to ascertain eligibility for inclusion. Studies identified as unclear will be checked to determine the eligibility of the study.

**Data collection process**

Data will be extracted from studies by two independent reviewers (RG and MMW) using a standardised extraction form, based on the Cochrane data extraction template23 as a guide and entered into a Microsoft Excel spreadsheet. The data extracted will include study population (including age, gender, country, reason for colonoscopy), type of blood-based biomarker (eg, methylated DNA), test method (eg, serum vs plasma; analysis technique such as digital droplet PCR), type of study, number of participants, pathology details (eg, type of precancerous lesion, stage of CRC, how patients were classified as ‘healthy’ or without cancer) and outcomes of significance to the review objectives (ie, the sensitivity/specificity of the blood-based biomarker for colonic adenomas/sessile lesions as well as CRC and non-neoplastic controls). Data extraction domains will involve: (1) article details (author, title, country of origin), (2) population, (3) methods and (4) results. A standardised extraction sheet will be tested for completeness on a subset of studies, after which any relevant updates will be made prior to full extraction of all eligible studies. The extracted data will be reviewed for accuracy by TJHL and any discrepancies discussed and resolved as a group.

**Data items**

A summary of data items to be extracted from included studies is outlined in table 2, where data are not identifiable or unclear, attempts will be made to contact the corresponding author for clarification. On attempts to contact the author being unsuccessful within a set timeframe and the clarification potentially having an impact on the eligibility, the study will be deemed ineligible based on ambiguity. If there is evidence of overlapping samples, where the same cohort appears to have been used for multiple studies, the authors will be contacted to confirm eligibility. Where other types of biomarkers (eg, tissue-based biomarkers) or blood-based biomarkers used for other advanced cancers are used, only the blood-based biomarkers specific to colonic advanced precancerous lesions (and CRC) will be used for extraction.

**Risk of bias**

A formal risk of bias assessment will be conducted via the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies version 2) tool, as recommended in the Cochrane Handbook,23 which is used for evaluating potential bias (quality appraisal) of studies assessing diagnostic test accuracy. The following domains will be assessed: (1) patient selection, (2) type of blood biomarker, (3) reference

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**Table 2** Summary of items to be extracted from eligible studies using the standardised extraction form

| Information area | Data extracted |
|------------------|----------------|
| **Background**   | Authors, Year of publication, Name of the blood-based biomarker, Blood-based biomarker type (eg, cfDNA, miRNA etc.) |
| **Methodology**  | Specimen type (eg, serum vs plasma), Study type, Number of participants included, Cohort included (eg, no neoplasia detected, advanced adenoma, CRC), Technique used for blood-biomarker assay (eg, qPCR) |
| **Results**      | Accuracy of blood-based biomarker (sensitivity, specificity) for advanced adenoma/sessile serrated lesion, Accuracy of blood-based biomarker (sensitivity, specificity) for CRC |

CfDNA, circulating cell free DNA; CRC, colorectal cancer.
standard and (4) flow of patients through the study and
timing of the index test(s) and reference standard (‘flow
and timing’). The tool will be completed according to
four phases: (1) state the review question, (2) develop
review-specific guidance, (3) review the published flow
diagram for the primary study or construct a flow diagram
if none is reported and (4) judgement of bias and appli-
cability. Each domain will then be assessed in terms of the
risk of bias and the first three domains are also assessed
for applicability. To help reach a judgement on the risk of
bias, signalling questions will be included, such as ‘were
the participants representative of the general population
of those with advanced colorectal lesion?’ and “was there
an acceptable reference standard referred to?”. These
identify aspects of study design related to the poten-
tial for bias and aim to help reviewers make risk of bias
judgements.

Data synthesis

Studies will be synthesised using a best evidence synthesis.
Meta-analysis of diagnostic test accuracy can be carried
out; however, more sophisticated methods may be
required to simultaneously analyse outcome measures
(ie, sensitivity and specificity). Methods such as bivariate
model and hierarchical summary ROC model may be
carried out.

In order to be considered for meta-analysis, the
outcomes and the methodology of eligible studies must
maintain homogeneity. For example, they need to have
used the same type of test with the same type of compar-
tors (ie, a DNA methylation test for adenomas vs non-
cancer controls). The process for meta-analysis will be
more clear pending data extraction, based on assumptions
of homogeneity remaining true. The remainder of this
section is based on such an assumption of homogeneity in
outcomes and methodology of the studies; however, some
changes may be needed following data extraction.

The heterogeneity of the eligible studies will be assessed
according to outcome categories, such as:
1. The sensitivity of the test to detect precancerous lesion
(advanced adenoma and/or sessile serrated lesion).
2. The blood test methodology has been clearly de-
scribed.
3. The blood test considers the anatomical status (ie, dis-
tal vs proximal) of the precancerous lesion (advanced
adenoma/sessile serrated lesion).
4. The association between the blood test results and
pathological or histological features of the precancer-
ous lesion (advanced adenoma/sessile serrated le-
sion).
5. The association between the blood test results and
CRC status.
6. The assessment of factors influencing the accuracy of
the blood test.
7. The quality of the studies included according to the
QUADAS-2 tool.

Where homogeneity is sufficient between groups within
these categories, then inclusion within meta-analysis either
as a large group or several subgroups will be determined
by all authors. If the eligible studies are clearly homog-
enedous, then each reviewer will place studies into appro-
priate subgroups for analysis. This process will be done by
each reviewer independently to determine, which factors
will allow the best and most accurate comparisons to be
made. Relevant subgroupings are likely to be made based
on the methodological factors listed in table 2 above.

For example, subgroupings according to whether the
patient group(s) have different classifications of colonic
adenoma(s)/sessile serrated lesion(s) would be consid-
ered, as appropriate for the eligible studies. If suitable,
reviewers can include studies in more than one subgroup
(ie, different genomic analysis, different technique); how-
ever, in this instance, the subgroups will not be used
in the same meta-analysis. Where reviewers agree on what
is to be grouped for each meta-analysis, this process will
be carried out. If there is not broad consensus on the
groups, further discussion will take place. If the reviewers
disagree, the authors as a group will determine suitability
of meta-analysis or meta-synthesis.

On a meta-analysis being deemed appropriate by the
reviewers, a statistical test of heterogeneity will be carried
out, providing an I² value in the heterogeneity of the sample.36
The I² value will be reported as a percentage and interpreted as suggested in the Cochrane Handbook
for Systematic Reviews.23 Significance in the measure
of heterogeneity as calculated by the χ² test will be set
at p≤0.10. In the event significance was reported, the I²
statistic will be then explored to define the magnitude
of heterogeneity about the finding, where 0–40, 30–60,
50–90 and 75+ are suggestive of low, moderate, substan-
tial and considerable heterogeneity, respectively.23 In
the instance of statistical heterogeneity, leave-one-out sensi-
tivity analyses may be performed; however, groups consid-
ered to exceed the minimal value for heterogeneity will
be ineligible for meta-analysis and, hence, considered for
meta-synthesis instead.

Comparisons in some of the categories may be chal-
lenging to assess due to differences in biomarker selec-
tion as well as study design. Where meta-analysis has
been decided as appropriate by the group, results will
be extracted from the eligible studies and aggregated,
with changes normalised and reported as percentage
changes or standard mean differences in all studies.
Where data are lacking, the authors of relevant studies
will be contacted to provide further clarity on the data.
If the data are not sufficiently homogenous, a criti-
cal/narrative synthesis will be focused from the data
set alongside some binary elements of analysis. In this
context, statements such as ‘increase’, ‘decrease’ or ‘no
change’ in the accuracy of the proposed blood-based
biomarkers will be described.

Confidence in cumulative evidence

The potential of publication bias will be minimised
through a comprehensive search of unpublished studies,
contacting respective authors in the field and
including grey literature obtained via several further methods (eg, snowballing of primary and review article reference lists). Conference presentations not carried through to publication will also be reviewed, with authors contacted. Further statistical tests, such as the Begg and Mazumbar’s rank correlation test and Egger’s linear regression model, may be applied to each category and overall analyses. On publication bias being detected, Duval and Tweedie’s trim and fill correction may be applied, and the resultant effect sizes and 95% CIs examined in further detail.

The pooled data will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to evaluate the overall quality and ‘certainty of recommendations’ from the literature. The GRADE approach will be used to determine the certainty and strength of evidence according to the categories (methodological and outcome based/results) in table 2 and carried out in accordance with set recommendations. For example, observational studies will be assigned a ‘low’ certainty of recommendation prior to then either being upgraded or downgraded from this point, based on the quality of the evidence. Studies will be upgraded for factors such as large effect sizes or mean test positivity is associated with more aggressive precancerous lesions, blood-based biomarker characteristics and accuracy of the biomarker (sensitivity/specificity). Potential down-grading of studies for certainty of evidence may occur when there is substantial publication bias, indirect relationships with results (ie, unexplained confounding) or inconsistencies between studies. From this process, qualitative ratings for the certainty of evidence and recommendations will be listed as ‘high’, ‘moderate’, ‘low’ or ‘very low’ and able to be interpreted according to the GRADE approach.

ETHICS AND DISSEMINATION OF RESULTS

No patient data will be included in our review and, therefore, ethics approval is not required. It is anticipated that the review will identify the most promising candidate biomarkers for clinical translation in the screening for advanced precancerous lesions. The results will be published in a peer-reviewed journal and presented at appropriate domestic/international conferences.

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Contributors All authors have contributed to the focus of this systematic review topic and have reviewed each draft of the protocol and approved the final manuscript. Specifically, ELS and GY have been responsible for the initial conceptualisation of this work. TJHL, ELS, MMW, JMW and RG led the planning, design as well as the conduct and reporting of this manuscript. All authors made substantial contributions to the drafting and critical revision of the work and all authors approved the final manuscript.

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Competing interests GYP has a consultancy arrangement with a company that has developed a blood test for CRC detection (Clinical Genomics).

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Patient consent for publication Not applicable.

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