THE PSYCHOLOGICAL IMPACT AND CLINICAL OUTCOMES ASSOCIATED WITH TESTING FOR OVARIAN CANCER IN SYMPTOMATIC WOMEN

By

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ABSTRACT

Aims: To investigate the psychological and clinical impact of symptom-triggered testing for ovarian cancer (OC).

Method: To investigate the psychological impact of symptom triggered testing for OC, a systematic review (SR) was undertaken to identify variables that were associated with psychological morbidity in patients undergoing testing for any cancer. The association between variables identified in the SR and anxiety and distress levels in women undergoing diagnostic testing for OC was subsequently explored in the dataset from a single-arm prospective diagnostic test accuracy study (Refining Ovarian Cancer Test accuracy Scores (ROCkeTS). To estimate the prevalence of psychological morbidity following testing for OC. To investigate the clinical benefit of symptom triggered testing for OC, the true positive rate of OC diagnosis by age, menopausal status and referral pathway was estimated in the ROCkeTS dataset. Finally, the oncological outcomes (performance status, stage at diagnosis, cytoreduction rate, extent of disease) in women diagnosed with high grade serous OC, the most lethal form of OC was evaluated.

Results: Findings from our SR demonstrated that the contribution of some factors to anxiety in cancer testing and their specificity of effect remain inconclusive. Targeting young women or those who are unemployed or who have low levels of educational attainment may offer a means to mitigate anxiety. Some studies suggested that one-stop clinics and patient navigators may be beneficial to mitigate anxiety. Most women experienced moderate-to-severe distress and anxiety following a referral for OC testing. The severity of anxiety and distress levels remained unchanged or worsened

in the majority of women at 12 months post OC testing despite a non-cancer diagnosis. Younger women and those who presented via the emergency pathway reported higher distress levels but were less likely to receive a diagnosis of OC. Symptom triggered testing facilitates the diagnosis of high grade serous OC at an early stage when women are in generally good health. Even in women with advanced stage OC, the tumour load is relatively not extensive and complete surgical clearance can be achieved in a high proportion.

Conclusion: Younger women have a lower risk of developing OC but are at especially high risk of psychological harm from testing and should be targeted for support. Improving awareness of the symptoms of OC will facilitate the institution of early investigations and evidence demonstrates that surgical intervention at an early stage improves outcomes.

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LIST OF ABBREVIATIONS

CA125	Cancer Antigen 125
COS-BC	Consequences of Screening–Breast Cancer
COS-LC	Psychosocial consequences of lung cancer screening
CRF	Case Report Form
CRI	Coping Resources Inventory
DOvE	Diagnosing Ovarian cancer Early
FIGO	International Federation of Obstetrics and Gynecology
FN	False Negative
FP	False Positive
FPQ-III	Fear of Pain Questionnaire-III
GHQ	General Health Questionnaire
GP	General Practitioner
HADS	Hospital Anxiety and Depression Scale
HPV	Human Papilloma Virus
HRT	Hormone Replacement Therapy
IES	Impact of Events Scale
IOTA	International Ovarian Tumour Analysis
JBI	Joanna Briggs Institute
LEEP	Loop Electrosurgical Excision Procedure
MBSS	Miller Behavioral Style Scale
MUIS	Mishel Uncertainty in Illness Scale
NHS	National Health Service
NICE	National Institute of Clinical Excellence
OC	Ovarian Cancer
PANAS	Positive and Negative Affect Schedule
PCQ	Psychological Consequences Questionnaire
PICO	Patient, Intervention, Comparator, Outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO	International prospective register of systematic reviews.
PTSD	Post Traumatic Stress Disorder
RCT	Randomised Controlled Trial
RMI	Risk of Malignancy Index
RoB2	Risk of Bias 2
ROCA	Risk of Ovarian Cancer Algorithm
ROCkeTS	Refining Ovarian Cancer Test Accuracy Scores
ROMA	Risk of Malignancy Algorithm
SD	Standard deviation
SF-12	Short Form-12
SPIDER	Sample, Phenomenon of Interest, Design, Evaluation, Research type
SR	Systematic Review
STAI	State-Trait Anxiety Inventory
STIC	Serous Tubal Intraepithelial Carcinoma
TVS	Transvaginal Ultrasound Scan
UKCTOCS	United Kingdom Collaborative Trial of Ovarian Cancer Screening
USS	Ultrasonography
VAS	Visual Analogue score

PUBLICATIONS AND PRESENTATIONS

Papers accepted for publication from this doctoral research

Kwong FL, Davenport C, Sundar S. Evaluating the Harms of Cancer Testing-A Systematic Review of the Adverse Psychological Correlates of Testing for Cancer and the Effectiveness of Interventions to Mitigate These. *Cancers (Basel).* 2023 Jun 25;15(13):3335. doi: 10.3390/cancers15133335. (Chapter 2)

Kwong FL, Kristunas C, Davenport C, Aggarwal R, Deeks J, Mallett S, Kehoe S, Timmerman D, Bourne T, Stobart H, Neal R, Menon U, Gentry-Maharaj A, Sturdy L, Ottridge R, Sundar S; ROCkeTS collaborators. Investigating harms of testing for ovarian cancer - psychological outcomes and cancer conversion rates in women with symptoms of ovarian cancer: A cohort study embedded in the multicentre ROCkeTS prospective diagnostic study. *BJOG*. 2024 Mar 31. doi: 10.1111/1471-0528.17813. Epub ahead of print. PMID: 38556698. (Chapter 3)

Kwong FL, Kristunas C, Davenport C, Deeks J, Mallett S, Agarwal R, Kehoe S, Timmerman D, Bourne T, Stobart H, Neal R, Menon U, Gentry-Maharaj A, Brenton J, Rosenfeld N, Sturdy L, Ottridge R, Sundar S on behalf of ROCkeTS collaborators. Symptom-triggered testing detects early stage and low volume resectable advanced stage ovarian cancer. Accepted for publication in the *International Journal of Gynecological Cancer (IJGC)*. (Chapter 4)

Published conference abstract arising from this doctoral research

Kwong F, Kristunas C, Davenport C, et al. (2022). ESGO. Anxiety and post-traumatic stress disorder in women referred after symptom triggered testing for ovarian cancer – analysis from the large multicentre national UK ROCkeTS study. *International Journal of Gynecologic Cancer.* 2022;32:A313-A314. (Chapter 3)

Related publications and presentations during this doctoral research

Kwong F, Kristunas, C, Davenport C, Sundar S. 2022). Investigating the psychological harms of testing for ovarian cancer in symptomatic women – results from the ROCkeTS study. Stakeholder workshop - Primary care and secondary care Diagnostic pathways for Ovarian cancer. (Chapters 2 and 3)

CHAPTER 1

INTRODUCTION

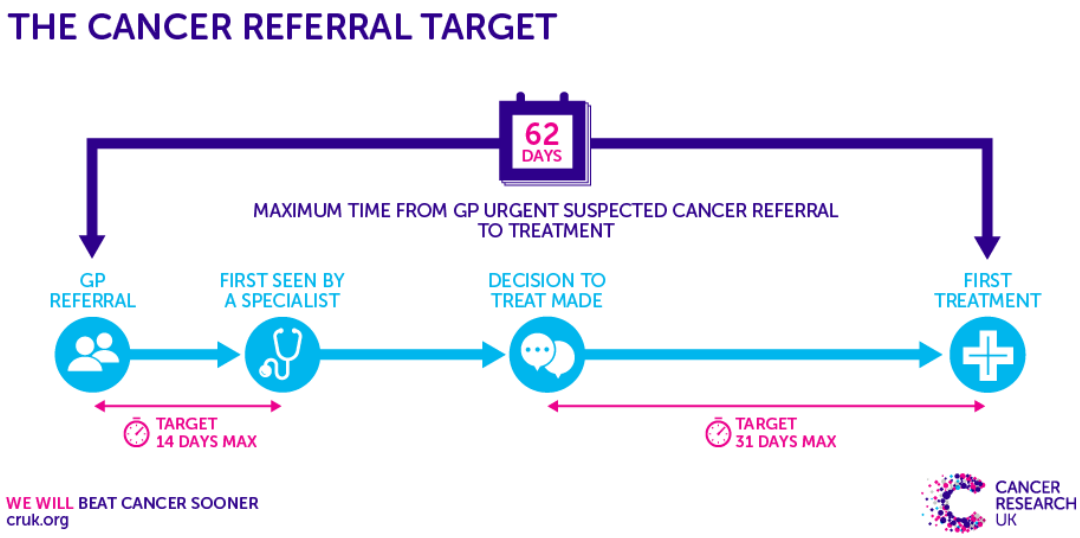
Screening versus Symptom-Triggered Testing in Ovarian Cancer

Ovarian cancer (OC) is the sixth most common cancer in women in the UK, and over 7000 new cases are detected every year (CRUK). Early-stage diagnosis is a robust predictor of survival. Most (95%) women diagnosed with OC in its earliest stage (Stage 1) will survive their disease for 5 years whilst this is true for only 15% of women diagnosed with Stage 4 disease (CRUK). One of the ambitions of the NHS Long Term Plan is to improve early stage (Stage 1 and 2) diagnosis of high-mortality cancers including OC from 50% to 75% by 2028 (NHS-England, 2019). Screening women prior to the onset of symptoms to detect OC at an early stage has demonstrated disappointing results from major randomised controlled trials which have not shown a significant reduction in mortality (Buys et al., 2011, Jacobs et al., 2016).

There is evidence that symptoms precede a diagnosis of OC by between 3 and 36 months (Goff et al., 2007, Goff et al., 2004, Bankhead et al., 2005, Smith et al., 2005). Goff et al (Goff et al., 2004) report a mean duration of symptoms of 3 to 4 months for symptoms such as abdominal pain and swelling. Complete tumour resection and low residual disease load after surgery, which may be achieved by early detection, is associated with increased survival in OC (Hoskins et al., 1994). Symptom-triggered testing for OC has therefore been advocated by several guidelines including NICE and the Society of Gynaecological Oncologists in the United States (Jacobs et al., 1999). In the UK, women who present to their GPs with symptoms suggestive of OC are recommended to undergo diagnostic investigations – a blood test for tumour marker CA125 and a transvaginal ultrasound scan (NICE, 2011). NICE recommends that women who have a raised CA125 level and an

abnormal ultrasound scan result (as interpreted by the GP) are to be referred through the 2 week wait pathway to secondary care (Figure 1). In practice, patients often require additional investigations including further imaging, image-guided biopsies, a referral to other specialties followed by a re-discussion of their case at the multidisciplinary team meeting before a decision to treat is reached. This process may therefore incur additional 'delays' in the patient's care pathway.

Figure 1. The Cancer Referral Target (Cancer Research UK)



The effectiveness of symptom-triggered testing for OC survival and mortality has not been evaluated.

An analysis of 2185 patients before and after the introduction of symptom-triggered testing in the UK suggested no effect of symptom-triggered testing on the stage at which OC was diagnosed (Rai et al., 2015). However, the authors cautioned that the lack of stage-shift could be attributed to a high proportion of inappropriate referrals. The indications for further testing by the General Practitioners varied greatly and did not adhere to the NICE guidance in many cases. The DOvE study (Gilbert et

al., 2012), a large prospective study of facilitated prompt assessment of symptomatic women over 50 years demonstrated a higher proportion of completely resectable ovarian cancers detected compared to women accessing symptom-triggered testing in the normal way (Gilbert et al., 2012). This pilot study involved an intense media campaign to disseminate information about symptoms associated with OC and compared outcomes between two groups of women: symptomatic women who self-referred or were referred by their family doctors to one of the DOvE centres, and those who had been referred to the Gynaecological Oncology Centre by their family doctors, gynaecologist, or other specialist. One of the recognised limitations of the DOvE study is that their participants were predominantly comprised of young, White and educated women who had been stimulated to seek medical attention through an intense media-awareness campaign. The authors acknowledged this limitation and its impact on the generalisability of their results, and plan to set up a network of satellite clinics which would be more accessible for older and less-educated women in the future.

The Psychological impact of Testing for cancer

The context of testing for cancer can be considered under two broad categories: screening and diagnostics. Screening usually refers to routine testing in asymptomatic average risk individuals. Diagnostic tests refer to testing in symptomatic or otherwise at-risk individuals. It therefore follows that the impact of screening and diagnosis on individuals would be expected to be different: in a screening population people believe themselves to be well and may therefore be at more significant risk of potential psychological harm compared to a diagnostic population. Anxiety has been demonstrated in women attending for OC screening

(Barrett et al., 2014). A scoping search did not identify studies specifically evaluating the psychological impact of symptomatic diagnostic testing for OC, particularly for women with a false positive result that is women referred for testing who do not receive a diagnosis of OC.

Although the literature for cancer screening and testing generally focuses on the impact of false negative results (missed diagnoses), false positives are more likely to be common than false negative results during screening and testing in low-risk groups, or early in the diagnostic pathway where the prevalence of cancer is low. Aside from generating anxiety, a false positive result may lead to repeat testing, biopsies or even surgery for affected women. The psychological sequelae of a false positive may therefore be profound (Barrett et al., 2014).

The psychological impact of screening for OC has been researched in a large UK study of nearly 203 000 women (Jacobs et al., 2016). Although this study did not find a significant difference in anxiety levels in women who had undergone screening tests for OC compared to those who had not, they did reveal that women attending for repeat testing following an initial abnormal test result experienced marginally higher levels of anxiety (Barrett et al., 2014). One of the recognised limitations of the UKCTOCS study is that the participants were not representative of the general referred population: women who participated in the study were volunteers, 96.3% of all participants were White females, and there was a wide geographical variation in recruitment rates. These findings may therefore not be generalisable to a screening population.

In comparison to screening, the psychological impact of symptom-triggered testing remains under-researched. Symptoms suggestive of OC such as bloating, pelvic or abdominal pain and urinary symptoms are not specific for OC and may overlap with a range of other conditions such as the menopause and irritable bowel syndrome (Goff et al., 2007). This together with the low specificity of CA125 for the detection of early stage disease is likely to lead to a high rate of false positive results and hence, referrals which will impact on both women and the heathcare system (Jacobs et al., 1999).

Multiple predisposing factors for anxiety such as a family history of cancer, higher baseline levels of anxiety, and a lower level of education have been identified from screening studies for breast cancer (Gøtzsche and Nielsen, 2011, Haste et al., 2020).

In contrast, women recruited to the ROCkeTS study have not been incentivised to participate in were study. Rather, these subjects were opportunistically invited to enrol into the study at their outpatient appointments or during their hospital admissions and may therefore be more representative of the at-risk population.

An Outline to my thesis

Chapter 2 and Chapter 3 of my thesis addressed the psychological impact of testing for Ovarian Cancer (OC) while Chapter 4 describes the clinical outcomes in women who underwent diagnostic testing for OC. I initially undertook a systematic review in Chapter 2 to identify which variables were associated with psychological morbidity during cancer testing and the effectiveness of interventions to mitigate

these. The results of this systematic review were used to inform the next phase of my research that in the analysis of the dataset from the ROCKETS study, a prospective longitudinal test accuracy study aiming to validate new risk scores in women with symptoms suggestive of OC, in Chapter 3. The aim of this study was to improve attendance for testing in hospital in women who present to their GPs with non-specific symptoms.

I formulated two distinct questions for the literature review in Chapter 2: (1) what bio (cancer type and testing method), psychosocial (patient characteristics), or healthcare organisational factors are associated with psychological outcomes of cancer testing, and (2) what interventions are effective at reducing adverse psychological outcomes associated with cancer testing? A preliminary scoping review highlighted that the literature surrounding the psychological impact associated specifically with OC diagnosis is scarce. I subsequently expanded the search criteria to include diagnostic testing for any cancer and for any testing application: screening or diagnosis. The studies were largely heterogeneous in terms of tests, measurement tools used, definitions of psychological morbidity and cancer types. However, despite the heterogeneity, there were some variables that were associated with psychological morbidity. A few studies suggested that one-stop clinics and the introduction of patient navigators may be helpful to reduce anxiety in patients attending for cancer testing. For the purpose of this thesis, I have interpreted ‘psychological distress’ as any unpleasant emotion which has a negative impact on the mental wellbeing of an individual. The results of the systematic review are presented in Chapter 2.

The next stage was to analyse the ROCkeTS dataset to identify whether the variables identified during my systematic review were similarly associated with anxiety and distress levels in women attending for OC testing. Although some studies have suggested that women may suffer from the long-term effects associated with the testing process, irrespective of the final diagnosis, there was a paucity of studies describing its effects in women attending for OC testing. I therefore explored whether anxiety and distress persist in women whose initial investigations are suggestive of cancer but in whom the latter is later disproved following more conclusive results. ROCkeTS utilised two validated self-administered questionnaires to measure levels of anxiety and distress: the STAI-6 (Spielberger CD, 1983) and IES-r questionnaires (Weiss DS, 1997) respectively. In both of these, there is a positive correlation between scores and levels of anxiety and distress. Results of my analysis showed that women presenting for testing experience moderate to severe anxiety and distress. In women without a cancer diagnosis this psychological distress persists at 12 months. Younger women reported higher levels of anxiety and distress at recruitment into the ROCkeTS study. Paradoxically, the prevalence of OC is lower in younger women. Our results therefore provide an impetus to prompt an urgent review of the current 'one-size fits all criteria' for OC testing to minimise psychological sequelae in women referred for the diagnosis of OC. The results of this analysis are presented in Chapter 3.

OC is a largely heterogeneous disease and comprises of many subtypes. High grade serous OC, a rapidly progressive disease, accounts for half of all cases of OC but 90% of all OC deaths (NDRS, 2024). Currently, various strategies are aimed to reduce the risk of developing OC. These include the opportunistic removal of the

fallopian tubes in women undergoing pelvic surgeries for benign conditions, or risk-reducing surgeries to remove the fallopian tubes and ovaries in premenopausal women who carry a BRCA1/2 gene mutation (Hanley et al., 2022, Kotsopoulous et al., 2016). The benefits of symptom-based testing are disputed on the basis that the disease is already in its advanced stages once women present with symptoms to their doctors and therefore the effectiveness of treatment is reduced (Nagle et al., 2011). In Chapter 4, I analysed the surgical outcomes in women who were recruited to the ROCkeTS study for via the fast-track pathway. This pathway, also referred to as the two week wait pathway, represents an urgent referral route whereby women presenting with symptoms are expedited for further testing. Results of this analysis demonstrated that symptom-based testing detects OC, including the high grade serous subtype when the disease is less widespread. This finding is clinically significant as a less extensive disease spread is associated with a higher rate of complete disease clearance, and hence superior oncological outcomes, especially survival (Hoskins et al., 1994). As a result, uptake of the fast-track pathway should be advocated in symptomatic women as it may improve oncological outcomes and reduce OC related mortality.

CHAPTER 2

EVALUATING THE HARMS OF CANCER TESTING-A SYSTEMATIC REVIEW OF THE ADVERSE PSYCHOLOGICAL CORRELATES OF TESTING FOR CANCER AND THE EFFECTIVENESS OF INTERVENTIONS TO MITIGATE THESE

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Abstract

Background: Several studies have described the psychological harms of testing for cancer. However, most were conducted in asymptomatic subjects and in cancers with a well-established screening programme. We sought to establish cancers in which the literature is deficient, and identify variables associated with psychological morbidity and interventions to mitigate their effect.

Methods: Electronic bibliographic databases were searched up to December 2020. We included quantitative studies reporting on variables associated with psychological morbidity associated with cancer testing and primary studies describing interventions to mitigate these.

Results: Twenty-six studies described individual, testing-related, and organisational variables. Thirteen randomised controlled trials on interventions were included, and these were categorised into five groups, namely the use of information aids, music therapy, the use of real-time videos, patient navigators and one-stop clinics, and pharmacological or homeopathic therapies.

Conclusions: The contribution of some factors to anxiety in cancer testing and their specificity of effect remains inconclusive and warrants further research in homogenous populations and testing contexts. Targeting young, unemployed patients with low levels of educational attainment may offer a means to mitigate anxiety. A limited body of research suggests that one-stop clinics and patient navigators may be beneficial in patients attending for diagnostic cancer testing.

Keywords: anxiety, cancer, diagnosis, harm, interventions, psychological

Introduction

Medical tests to detect cancer are key to improving early diagnosis and improving oncological outcomes, including patient survival. The Faster Diagnostic Framework was set up by NHS England in the U.K. in 2015 to fast-track patients with a possible diagnosis of cancer (NHS-England, 2019). One of the aims of this initiative is to reduce anxiety associated with prolonged waiting times, especially for patients irrespective of their diagnosis. Although testing is commonly viewed as beneficial, testing can cause harm. Harms associated with testing may be direct (for example pain associated with the test application and anxiety) or indirect, for example the harms associated with the downstream consequences of a test result including test errors (false positives and false negatives).

The context of testing (screening or diagnosis) and the place of a test in the clinical pathway (early or late) will determine the nature and importance of downstream indirect consequences. Screening usually refers to routine testing in asymptomatic average risk individuals to evaluate their risk of developing cancer. Diagnostic tests, in contrast, principally refer to testing to determine whether at-risk individuals actually have cancer. Whilst the purpose of screening and diagnostic tests are different, it follows that a screening test may lead to diagnostic testing in individuals who are identified as being at increased risk of developing cancer. For example, a missed cancer diagnosis (false negative, FN) may be afforded greater importance than a false positive (FP) result for an individual undergoing diagnostic testing. However, when tests are applied in low-prevalence populations such as in screening, the consequences of a missed cancer diagnosis (FN) need to be balanced against the consequences of receiving an FP for a larger absolute number

of individuals. Research to date has largely concentrated on the therapeutic, financial, psychosocial, and legal implications that occur as a result of cancer-screening programmes (Petticrew et al., 2000). In contrast, the consequences associated with diagnostic testing for cancer have received less attention.

There is compelling evidence that a negative testing experience per se may have a detrimental impact on patient satisfaction and reduce motivation to engage with healthcare services or attend for further testing or treatment. Studies have demonstrated a potential link between the level of psychological distress and the strength of the body's immune system (Ando et al., 2011, Witek-Janusek et al., 2007).

With various initiatives that will result in an increase in the number of individuals undergoing diagnostic testing for cancer, it is important to understand the potential psychological impacts of testing policy. In addition, determining whether certain individuals are more vulnerable to the adverse psychological effects of testing would allow targeting of interventions to mitigate these.

Existing research

We sought to identify any systematic review concerned with quantifying the psychological associations of cancer testing and the effectiveness of interventions to mitigate this. A scoping search conducted in December 2020 across systematic reviews evaluating the psychological associations of cancer testing across Ovid MEDLINE and Embase yielded a single quantitative review (Chad-Friedman et al., 2017) which examined the levels of anxiety, stress, worry, panic, and fear associated with screening tests for breast, colon, prostate, and lung cancers pre-test, post-test,

and post-negative-test results. Only studies conducted in the United States and published between 1946 and October 2016 were included. The authors excluded studies about cancer testing in a diagnostic context and confined their review to examination of the consequences of positive test results.

We therefore undertook a review with the aim of addressing deficiencies in the literature apropos of an up-to-date review without geographical restriction considering the psychological associations of testing for cancer and the potential effects of the entire testing process (pre-, during, and post-) regardless of test result. We also sought to ascertain evidence about interventions that mitigate anxiety in individuals undergoing cancer testing. Through this review, we also aim to highlight which cancers have been the most well-researched to date and thereby identify the types of cancer where a paucity of evidence prevails and where further research is mandated.

We anticipated a paucity of the literature concerned with diagnostic testing as opposed to screening and therefore decided to include both types of test application in our review scope. Whilst we hypothesised that there may be overlap in mechanisms of psychological associations and effectiveness between screening and diagnosis, we acknowledged potential differences by test application by distinguishing these in our synthesis.

Materials and Methods

Review Questions and Inclusion Criteria

Two separate frameworks for question formulation were used: SPIDER (Cooke et al., 2012) for question 1, as this was concerned with a phenomenon that

could be evaluated using diverse research approaches, and PICO for question 2, which is concerned with the examination of the effectiveness of interventions.

Question components are illustrated in Box 1.

Box 1

Inclusion criteria for questions 1 and 2.

Question 1
Sample: *Adults.*
Phenomenon of interest: *Testing for cancer (any type).*
Design of studies: *Cross-sectional, longitudinal (cohort), and mixed-method studies.*
Evaluation: *Any measure of psychological burden such as worry, anxiety, fear, distress, depression, and uncertainty measured via tools including but not restricted to STAI, HRQoL, SF-12, SF-36, and HADS.*
Research type: *Quantitative (cross-sectional, case control, and cohort) and mixed-methods, primary studies, or systematic reviews.*

Question 2
Population: *Adults undergoing diagnostic testing for any type of cancer.*
Intervention: *Any intervention(s) to improve psychological burden such as worry, anxiety, fear, distress, depression, and uncertainty measured via tools associated with testing for cancer.*
Control: *No intervention(s) or alternative intervention(s), including standard care.*
Outcome: *Any measure of psychological burden such as worry, anxiety, fear, distress, depression, and uncertainty measured via tools incuding but not restricted to STAI, HRQoL, SF-12, SF-36, and HADS.*
Study Design: *Systematic reviews of RCTS or RCTs.*

(1) What are the effects of individual characteristics, characteristics of the testing process, and healthcare organisational factors on the psychological associations of cancer testing?

(2) What interventions are effective at reducing the adverse psychological associations of cancer testing?

Search Strategy

Electronic bibliographic databases were searched using a combination of MESH and free-text terms combined using Boolean operators (and/or). OVID MEDLINE, PubMed, Embase, the Cochrane Library, and ClinicalTrials.gov were searched for published articles, and the British Library, Library Hub Discover, Opengrey.eu, the Grey Guide, gov.uk (news and communications), and the National Grey Literature Collection for unpublished literature. Electronic database searches were supplemented with searches of reference lists of included systematic reviews and primary studies. All articles from inception to December 2020 were included. Only articles published in English were included. The search strategy is available as an appendix. This systematic review was prospectively registered on PROSPERO (Registration number CRD42022321906).

Study Selection

Titles, abstracts, and full texts of potentially relevant titles and abstracts were screened by one reviewer against predefined inclusion criteria (Box 1), and reasons for exclusion of studies were documented using a PRISMA flow diagram (Figure 1).

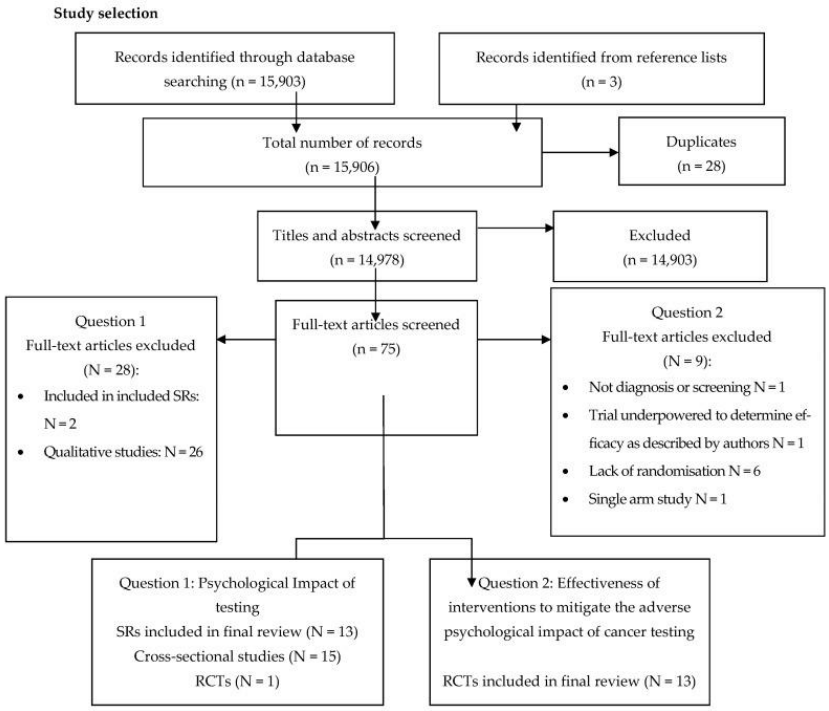

Figure 1. PRISMA flow diagram

Data Extraction

A single data extraction form was designed for questions 1 and 2. Data extracted included title, first author, year of publication, study design, aim of study, number of studies/participants, population characteristics, cancer type under investigation, test, intervention (where appropriate), comparator (where appropriate), and results.

Quality Assessment

For quality assessment of systematic reviews, five criteria drawn from the Joanna Briggs Institute (JBI) Checklist for Systematic Reviews and Research Syntheses were assessed, namely, the inclusion of a clear, focused question, clear

question formulation, comprehensive search strategy, quality assessment of studies, and data extraction by two independent reviewers (JBI, 2017b).

For cross-sectional studies, a modified JBI Checklist for Analytical Cross-Sectional Studies (JBI, 2017a) was used: the domain ('was the exposure measured in a valid and reliable way') was not considered relevant to this review question and was omitted. For RCTs, the Cochrane Risk of Bias 2 (RoB 2) tool (Cochrane, 2022) was employed.

We did not identify any cohort or mixed-method studies to include in this review. Quality assessment of primary studies was undertaken in duplicate by FK and CD.

Data Synthesis

Data synthesis was narrative and supported by tables to map similarities and differences in population, cancer, test type, intervention (where applicable), and outcomes for each of questions 1 and 2. Recognising that psychological associations are likely to be different in screening compared to diagnostic applications of testing, these different testing applications were considered separately for the purposes of synthesis.

On the basis of research identified as part of our scoping review of the predictors of anxiety associated with diagnostic and screening tests (Chorley et al., 2017, James et al., 2017, Kerrison et al., 2021), we used three themes as the framework for the synthesis of this review: individual characteristics, testing-related factors, and organisational factors.

Results

Volume of Studies

Question 1: Psychological associations of testing

A total of 26 studies, including 10 systematic reviews (SRs), 15 cross-sectional studies, and 1 randomised controlled trial (RCT) were identified. Of the 10 SRs, testing was undertaken for screening (7 studies), diagnosis (2 studies), or both (1 study). Nine primary studies were concerned with screening whilst seven were concerned with diagnostic testing.

Question 2: Effectiveness of interventions to mitigate adverse psychological associations of testing.

Thirteen randomised controlled trials (RCTs) were included. Interventions were undertaken for screening (five studies) and diagnosis (eight studies).

Characteristics of Included Studies

Question 1: Psychological associations of testing.

SRs from the following countries were included: U.S.A. (five), Finland (one), Australia (one), Ireland (one), The Netherlands (one), and Canada (one). The total number of studies included in each SR (qualitative and quantitative) ranged from 7 to 59, and the number of subjects ranged from 872 to 199,906. Most SRs focused on single cancers, namely, breast (three), cervical (two), colorectal (two), pancreatic (one), and lung (one), whilst one included various cancers.

Quantitative primary studies from Europe (eight), the U.S.A. (three), Taiwan (one), Australia (one), Oman (one), Canada (one), and Lebanon (one) were included. The number of subjects ranged from 31 to 3671. Studies were concerned with testing for cancer of the cervix (seven), breast (six), prostate (one), and ovary (two). Studies included a variety of tests, and different elements of the testing process including mammography (four), colposcopy (four), notification of abnormal cervical smear results (three), biopsy (two), transvaginal ultrasound scan (two), and HPV testing (one). The severity of psychological outcomes was measured at different time points including before testing (four), on the day of testing (seven), and immediately after testing or after receiving the test results (five). Psychological associations were assessed through various validated tools such as PCQ, STAI, COS-BC, SF-12, HADS, and MBSS, as well as author-designed questionnaires, or a combination of these.

Question 2: Effectiveness of interventions to mitigate adverse psychological associations of testing.

RCTs from the U.S.A. (five), Europe (five), Australia (one), Cameroon (one), and Thailand (one) were included. The number of participants ranged from 16 to 838. Interventions were associated with mammography for breast cancer (two studies), diagnostic or interventional colposcopy for cervical cancer (six studies), colonoscopy and flexible sigmoidoscopy for bowel cancer (one study), faecal occult blood test for bowel cancer (one study), a combination of different tests (one study), and biopsies (two studies).

Quality Assessment

Question 1: Psychological associations of testing (Table 1 and Table 2)

Aside from three reviews (Metsälä et al., 2012, Montgomery and McCrone, 2010, Nagendiram et al., 2020) where it was unclear whether the data extraction and quality assessment had been conducted in duplicate, SRs were considered at low risk of bias on the remaining four quality criteria (Table 1).

In the 15 included cross-sectional studies, all clearly defined the inclusion criteria, study subject, and settings, described how the psychological outcomes were measured, and processed the results using appropriate statistical analysis. Of these studies, 12/15 (80%) utilised validated measurement tools, while 3/15 (20%) measured outcomes using open-ended questions concerning the patients' emotions in addition to quantitative measurements. Only 1/15 (7%) of studies reported on confounders (Table 2).

Table 1. Quality assessment for systematic reviews for question 1 (adapted from the Joanna Briggs Institute (JBI) Checklist for Systematic Reviews and Research Syntheses)

	Clear focused question	Comprehensive search strategy†	- Explicit criteria for paper inclusion -Two independent reviewers	-Explicit criteria for quality assessment -Explicit criteria for data extraction	Validated methods for data analysis	Description of methods included and reproducible
Cazacu, 2019	Yes	Yes	Yes	Yes	Yes	Yes
Chad-Friedman, 2017	Yes	Yes	Yes	Yes	Yes	Yes
Metsälä, 2011	Yes	Yes	Yes	Yes to selection NA to two reviewers	Yes	Yes
Montgomery, 2010	Yes	Yes	Yes to selection NA to two reviewers	Yes to selection NA to two reviewers	Yes	Yes
Nagendiram, 2018	Yes	Yes	Yes	Yes to selection NA to two reviewers	Yes	Yes
Nelson, 2016	Yes	Yes	Yes	Yes	Yes	Yes
O'Connor, 2016	Yes	Yes	Yes	Yes	Yes	Yes
Van der Veld, 2017	Yes	Yes	Yes	Yes	Yes	Yes
Wu, 2016	Yes	Yes	Yes	No	Yes	Yes
Yang, 2018	Yes	Yes	Yes	Yes	Yes	Yes

†*The authors provided evidence of a logical and reproducible search strategy which identified the PICO components of the question. More than one citation database including grey literature was searched.*

Table 2. Quality assessment for cross-sectional studies for question 2 (using the JBI Checklist for Analytical Cross Sectional Studies)

	Inclusion criteria clearly defined	Study subjects and setting were clearly defined	Exposure measured in valid and reliable way	Measurement of condition (were patients selected according to strict definitions)	Confounders identified	Strategies to deal with confounders identified	Outcomes measured in valid and reliable way	Appropriate statistical analysis
Al-Alawi, 2019	Yes	Yes	NA	Yes	No	No	Yes	Yes
April-Sanders, 2018	Yes	Yes	NA	Yes	No	Yes	Yes	Yes
Bekkers, 2002	Yes	Yes	NA	Yes	No	Yes	Unclear	Yes
Bolejko, 2015	Yes	Yes	NA	Yes	No	Yes	Yes	Yes
Drolet, 2011	Yes	Yes	NA	Yes	No	Yes	Unclear	Yes
El Hachem, 2019	Yes	Yes	NA	Yes	No	Yes	Unclear	Yes
French, 2006	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes
Gray, 2006	Yes	Yes	NA	Yes	No	Yes	Yes	Yes
Kola, 2012	Yes	Yes	NA	Yes	No	Yes	Yes	Yes
Liao, 2008	Yes	Yes	NA	Yes	No	No	Yes	No
Maissi, 2004	Yes	Yes	NA	Yes	No	Yes	Yes	Yes
Medd, 2005	Yes	Yes	NA	Yes	No	Yes	Yes	Yes
O'Connor, 2016	Yes	Yes	NA	Yes	No	Yes	Yes	Yes
Wiggins, 2017	Yes	Yes	NA	Yes	No	Yes	Yes	Yes

	Inclusion criteria clearly defined	Study subjects and setting were clearly defined	Exposure measured in valid and reliable way	Measurement of condition (were patients selected according to strict definitions)	Confounders identified	Strategies to deal with confounders identified	Outcomes measured in valid and reliable way	Appropriate statistical analysis
Wiggins, 2019	Yes	Yes	NA	Yes	No	Yes	Yes	Yes

Question 2: Effectiveness of interventions to mitigate adverse psychological associations of testing (Figure 2)

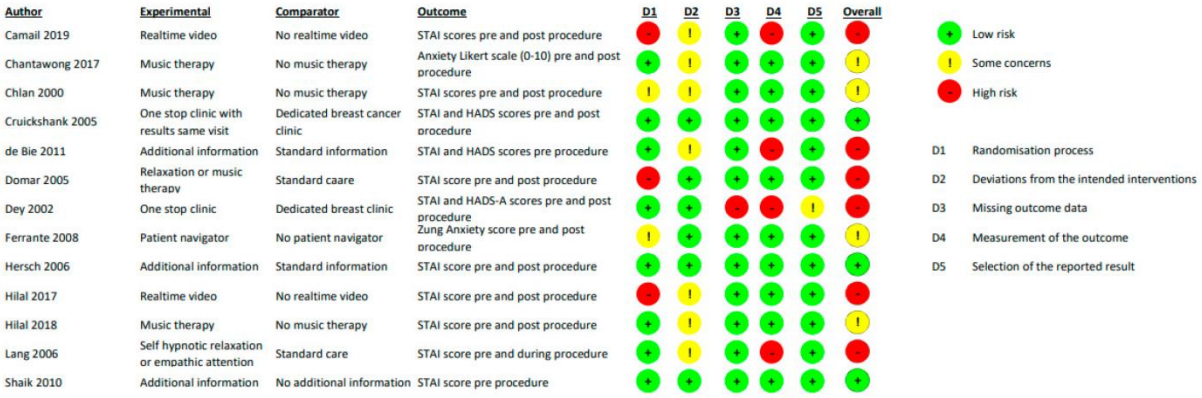

Figure 2. Quality assessment for randomised controlled trials for question 2 (using the Risk of Bias RoB2 tool).

(Camail et al., 2019, Chantawong and Charoenkwan, 2017, Chlan et al., 2000, Cruickshank et al., 2005, de Bie et al., 2011, Domar et al., 2005, Dey et al., 2002, Ferrante et al., 2008, Hersch et al., 2015, Hilal et al., 2017, Hilal et al., 2018, Lang et al., 2006, Shaikh et al., 2010)

A total of 46% (6/13) of the RCTs were at 'high' risk of bias, 31% (4/13) at 'some concerns', and 23% (3/13) at 'low' risk of bias. For those studies regarded as being at high risk of bias, this was attributed to two domains: the randomisation process and the outcome measurement. The studies were graded as 'low' or 'some concerns' for the risk of bias across the remaining domains because of one or more

deviations from the intended intervention, missing outcome data, and selective reporting of results.

Synthesis of Results

Question 1: Psychological associations of testing.

For synthesis, predictive factors were divided into three categories derived from themes identified in the literature. Included studies investigated the association of the following variables in each of the three predefined categories: psychosocial (age, ethnicity, educational status, personal or family history of cancer, employment status, perceived risk of cancer, presence of partner and children, social support, knowledge of cancer, smoking history, and intrinsic trait anxiety), testing-related factors (cancer site, previous abnormal result or severity of index result, procedure-related anxiety, and previous adverse experience of testing), and organisational factors (satisfaction with information received, waiting times, and communication of results).

Psychological outcomes including anxiety, depression, distress, or worry were measured using validated measurement tools such as STAI, HADS, Impact of Events Scale (IES), and General Health Questionnaire (GHQ). Individual reported levels of uncertainty, coping style, and expectations were assessed using various tools including the Psychological Consequences Questionnaire (PCQ), Consequences of Screening–Breast Cancer (COS-BC), Positive and Negative Affect Schedule (PANAS), Multi-Dimensional Health Locus of Control Scale (MHLCS), Miller Behavioral Style Scale (MBSS), and Mishel Uncertainty in Illness Scale (MUIS) questionnaires. Fear associated with the testing procedure was measured, e.g., pain

was measured using visual analogue scales (VAS) or the Fear of Pain Questionnaire-III (FPQ-III). Finally, the consequences of testing on patients' quality of life were examined using the EuroQol or Short Form-12 tools.

I. Individual (psychosocial) characteristics

1. Age

Screening

Two SRs (including seven studies (Cazacu et al., 2019) and seven studies (van der Velde et al., 2017) each) and three cross-sectional studies found a negative association between age and psychosocial morbidity in screening for breast (Al-Alawi et al., 2019, April-Sanders et al., 2017), pancreatic (Cazacu et al., 2019), cervical (Gray et al., 2006) and colorectal (van der Velde et al., 2017) cancers.

Four cross-sectional studies found no statistically significant association between age and psychological morbidity with cancer screening for breast (Bolejko et al., 2015, El Hachem et al., 2019), cervical (Drolet et al., 2012), or ovarian cancers (Wiggins et al., 2018).

Two SRs (with 2/15 studies including age as a variable (Metsälä et al., 2012) and 5/58 studies including age as a variable (Yang et al., 2018) in each study) reported conflicting results towards the associations of age on psychological morbidity in breast cancer (Metsälä et al., 2012) and colorectal cancer (Yang et al., 2018)screening.

Diagnosis

Three cross-sectional studies (Bekkers et al., 2002, Kola and Walsh, 2012, O'Connor et al., 2016) and one RCT (Hilal et al., 2017) in colposcopy for cervical cancer testing showed no correlation between age and levels of anxiety. One cross-sectional study in breast cancer (Liao et al., 2008) concluded that age was not a significant predictor for short- or long-term anxiety during the diagnostic phase for women with suspected breast cancer.

One SR including 30 studies (Montgomery and McCrone, 2010) reported the role of age as inconclusive.

2. Ethnicity

Screening

One SR (Nagendiram et al., 2020) on cervical cancer (13 studies), one SR (Chad-Friedman et al., 2017) on a combination of cancer types (22 studies), and one cross-sectional study on breast cancer (Bolejko et al., 2015) demonstrated that non-white or non-native women were at high risk of psychological distress compared to native or Caucasian women.

In one cross-sectional study on cervical cancer testing (Gray et al., 2006), ethnicity was not shown to be associated with anxiety following an abnormal cervical smear result.

Diagnostic

One cross-sectional study (O'Connor et al., 2016) demonstrated that non-Irish participants were at greater risk of anxiety from cervical cancer testing.

3. Education status

Screening

Three SRs (including 15 studies (Metsälä et al., 2012), 13 studies (Wu et al., 2016), and 58 studies (Yang et al., 2018) each and three cross-sectional studies showed a negative association between educational status and anxiety levels in breast (Metsälä et al., 2012, Bolejko et al., 2015), lung (Wu et al., 2016), cervical (Drolet et al., 2012), colorectal (Yang et al., 2018), and ovarian (Wiggins et al., 2018) cancer testing. One cross-sectional study (Al-Alawi et al., 2019) found no association between literacy levels and the magnitude of anxiety in women who underwent mammograms for breast cancer screening.

Diagnostic

One SR (Yang et al., 2018) on the associations of endoscopic procedures for CRC screening showed a negative correlation between education levels and levels of anxiety. Three cross-sectional studies did not find an association between educational level and anxiety in testing for cervical (Bekkers et al., 2002, Kola and Walsh, 2012) and breast cancer (Liao et al., 2008).

4. Previous experience of cancer

Screening

One SR (Wu et al., 2016) and two cross-sectional studies described a positive association between a family history of cancer and anxiety associated with testing across lung (Wu et al., 2016), breast (Al-Alawi et al., 2019), and ovarian (Wiggins et al., 2018) cancers.

A single study concerned with the association of previous cancer testing included in the SR by Metsälä (Metsälä et al., 2012) did not find an association between a family history of breast cancer and anxiety levels.

Diagnostic

Three studies concerned with the association of previous cancer testing in an SR by Montgomery (Montgomery and McCrone, 2010) demonstrated a statistically significant positive correlation between a history of breast cancer and reported levels of distress and anxiety among women awaiting a breast biopsy or curative surgery.

5. Employment

Screening

Two cross-sectional studies demonstrated a negative association between employment status and anxiety levels during breast (Al-Alawi et al., 2019) and cervical (Gray et al., 2006) cancer screening.

6. Perceived risk of cancer

Screening

One SR (Cazacu et al., 2019) in pancreatic cancer and three cross-sectional studies in breast cancer (April-Sanders et al., 2017, Bolejko et al., 2015, Maissi et al., 2004) showed a positive association between a perceived risk of cancer and testing.

Diagnostic

One cross-sectional study (Liao et al., 2008) demonstrated that a self-perceived probability of breast cancer was associated with statistically higher levels of anxiety before the biopsy but not after a diagnosis of breast cancer.

7. Social support including living with a partner

Screening

Two cross-sectional studies in breast (Bolejko et al., 2015) and cervical (Drolet et al., 2012) cancer screening demonstrated a positive association of social support on improved psychological outcomes. One cross-sectional study did not find an association between social support and anxiety levels in women following a false positive ovarian cancer screening result (Wiggins et al., 2018).

Diagnostic

Two cross-sectional studies in cervical cancer (Bekkers et al., 2002, Kola and Walsh, 2012) and one in breast cancer (Liao et al., 2008) demonstrated that having a partner was protective against anxiety with a statistically significantly lower mean state anxiety score.

Montgomery (Montgomery and McCrone, 2010), in their SR (30 studies), did not find an association between marital status and psychological distress.

8. Having children

Screening

One cross-sectional study in cervical cancer screening (Gray et al., 2006) showed that having children was associated with higher levels of anxiety following an abnormal cervical smear test.

Diagnostic

In one cross-sectional study on cervical cancer (Kola and Walsh, 2012), parous women were at higher risk of colposcopy-associated distress.

One cross-sectional study (Bekkers et al., 2002) and one RCT (Hilal et al., 2017) did not find a correlation between having children and its association on anxiety with colposcopy for cervical cancer.

9. Own knowledge of cancer

Screening

Three cross-sectional studies in breast (Bolejko et al., 2015) and cervical (Drolet et al., 2012, Maissi et al., 2004) cancers showed that a lack of knowledge about cancer had a positive association with anxiety levels.

10. Smoking status

Screening

One SR (Wu et al., 2016) in lung cancer (13 studies), one SR (Chad-Friedman et al., 2017) across various cancers, and two cross-sectional studies in cervical cancer (Drolet et al., 2012, Gray et al., 2006) showed a positive association between smoking status and anxiety levels with cancer testing.

Diagnostic

One RCT and one cross-sectional study demonstrated a positive correlation between smoking and colposcopy for cervical cancer (O'Connor et al., 2016, Hilal et al., 2017).

11. Trait or intrinsic anxiety and depression

Diagnostic

Five studies included in an SR by Montgomery (Montgomery and McCrone, 2010) showed that amongst women referred for colposcopy, those with higher baseline depression scores experienced higher levels of anxiety and depression as well as a greater fear of cancer at the two-year follow-up.

II. Test-related factors

1. Previous experience of testing including severity of initial result

Screening

Two SRs (including 15 studies (Metsälä et al., 2012) and 58 studies (Yang et al., 2018) each) and two cross-sectional studies (Drolet et al., 2012, El Hachem et al., 2019) reported a positive association between a previous adverse experience of testing and more severe initial results in breast cancer (Metsälä et al., 2012, El Hachem et al., 2019), CRC (Yang et al., 2018), and cervical cancer (Drolet et al., 2012). One cross-sectional study in cervical cancer (Gray et al., 2006) did not find an association between the index smear result or number of previous abnormal results and anxiety levels in cervical cancer testing.

Diagnostic

A positive association between a previous negative experience and anxiety levels in cervical cancer testing was demonstrated in one SR (O'Connor et al., 2016) (16 studies). Two cross-sectional studies concerned with colposcopy for cervical cancer, however, did not demonstrate an association between previous results and anxiety levels associated with them (Bekkers et al., 2002, Kola and Walsh, 2012).

2. Procedure-related

Intimate and invasive examinations have been significantly and positively associated with higher fear, worry, embarrassment, and worries about potential sequelae across breast, colorectal, lung and cervical cancers (Metsälä et al., 2012, Nagendiram et al., 2020, van der Velde et al., 2017, Yang et al., 2018, O'Connor et al., 2016). Various procedures such as HPV testing, colonoscopy, flexible sigmoidoscopy, and prostate needle biopsy were considered in these studies.

III. Organisational

Information about testing

Screening

One cross-sectional study showed that lower satisfaction levels with the information from healthcare professionals in women with a false-positive screening mammography for breast cancer (Bolejko et al., 2015) were significantly and positively associated with a greater sense of dejection, anxiety, and poorer sleep. In

another cross-sectional study (Drolet et al., 2012) on cervical cancer, women who received their abnormal smear results in person reported higher levels of anxiety than those informed by letter or telephone.

Diagnostic

A cross-sectional study by Bekkers (Bekkers et al., 2002) indicated that longer waiting times were statistically positively associated with anxiety in women attending for colposcopy for cervical cancer testing. The authors also concluded that there was a statistically significant association between satisfaction with the information from the GP or gynaecologist and the mean state anxiety scores in those women.

Conclusions for Question 1

Several variables were identified which could have positive correlations with anxiety levels in both screening and diagnostic testing for cancer, namely, being non-white or non-native, a perceived higher risk of developing a malignancy, lack of social support, a positive smoking history, and low educational attainments. In breast and cervical cancers, a lack of knowledge about cancer or the testing process was associated with higher anxiety levels in screening populations only. On the other hand, having a partner was protective in screening and diagnostic testing for cervical cancer. The effect of age was inconsistent even within the same cancer (i.e., some breast cancer studies showed lower age was associated with high anxiety levels, while others showed no difference) for both screening and diagnostic tests.

With regard to testing-related factors, the absence of a previous abnormal test result or the receipt of a severe initial screening result were associated with worse psychological outcomes in screening but not diagnostic testing for cervical and breast

cancers. Intimate or invasive modalities such as biopsy, colposcopy, or flexible sigmoidoscopy were associated with high anxiety levels during screening and diagnostic testing. A previous adverse experience of testing was associated with worse anxiety levels in breast, cervical, and colorectal cancer testing.

Finally, some organisational practices could be associated with higher anxiety levels: women who received their results in person and those who experienced longer waiting times for a colposcopy following abnormal smears reported higher anxiety levels. A lack of information about testing and subsequent lack of satisfaction also contributed to greater psychological morbidity.

Question 2. What interventions are effective at reducing the adverse psychological effects of cancer testing? (Table 3)

Table 3. Results of RCTS: Interventions to reduce psychological morbidity associated with cancer testing for question 2

Author, year	Cancer Test	Intervention (I)/ Control (C)	Measurement tools and assessment timepoints	Effect size
Camail, 2019	Cervix Visual inspection of cervix	I: Realtime video during (N=60) C: No realtime video (N=58)	<u>Measurement tools:</u> STAI <u>Timepoints:</u> Pre and post procedure	Δ mean (S.D) Difference in STAI score before and after intervention I: 7.9 (14.3.) C: - 4.2 (9.0), p-value =0.10
Chantaw ong, 2017	Cervix Loop *electrosurgic al excision* pro cedure (LEEP)	I: Music (N=74) C: No music (N=76)	<u>Measurement tools:</u> VAS <u>Timepoints:</u> Pre and post LEEP	Δ mean (S.D) I. Pre-biopsy I: 3.7 (2.6) C: 4.1 (3.0), p-value 0.38 II. Post-biopsy I: 4.0 (2.9) C: 4.7 (3.2), p-value .16

Author, year	Cancer Test	Intervention (I)/ Control (C)	Measurement tools and assessment timepoints	Effect size
Chlan, 2000	Colon Flexible sigmoidoscopy	I: Music during flexible sigmoidoscopy (N=30) C: No music during flexible sigmoidoscopy (N=34)	<u>Measurement tools:</u> STAI <u>Timepoints:</u> Pre and immediately post procedure	Δ mean (SD) Baseline state anxiety — I: 36.9(12.5) C: 40.2(11.9), p-value 0.28 Procedure state anxiety — I: 34.5(10.0) C: 41.8(13.5), p-value 0.02
Cruickshank, 2005	Cervix colposcopy	I: Self-administration of isoflurane and desflurane (N=198) C: Self-administration of placebo (N=198)	<u>Measurement tools:</u> HADS (anxiety subscale) <u>Timepoints:</u> - At baseline prior to treatment - Immediately posttreatment - 6 months after treatment but prior to receiving a colposcopy follow-up appointment	Δ mean (S.D) Baseline — I: 8.37 (4.15) C: 7.77 (3.97), p-value 'ns'* Immediately posttreatment — I: 7.30 (4.11) C: 7.29 (4.06), p-value 'ns' 6-month follow-up — I: 6.49 (4.19) C: 6.49 (4.27), p-value 'ns'
De Bie, 2011	Cervix Colposcopy	I: Individually targeted information (N=75) C: Standard care (N=74)	<u>Measurement tools:</u> - HADS - STAI <u>Timepoints:</u> Prior to colposcopy	Δ median (IQR) STAI — I: 33.0 (27.0–41.0) C: 33.0 (27.0–41.3), p-value 0.96 HADS anxiety — I: 5.0 (3.0–9.0) C: 6.0 (4.0–10.0), p-value 0.26
Dey, 2002	Breast Mammography, USS, aspiration cytology, same-day results and management plan.	I: One-stop clinics (N=267) C: Dedicated breast clinics with women asked to return the following week to discuss the results (N=211)	<u>Measurement tools:</u> - HADS (anxiety subscale) - STAI <u>Timepoints:</u> - Baseline (immediately before assessment) - STAI (24 hours after first visit) - HADS (three weeks and three months after diagnosis)	Δ mean (S.D) <u>STAI</u> Baseline — I: 48.1 (13.9) C: 47.2 (14.9) 24 hours — I: 34.5 (14.6) C: 39.8 (15.8), p-value<0.0001 <u>HADS</u> Baseline — I: 8.9 (4.4) C: 8.8 (4.9) Three weeks — I: 7.3 (4.7) C: 7.4 (4.3), p-value 0.55 Three months — I: 7.0 (4.6) C: 7.5 (4.7), p-value 0.22

Author, year	Cancer Test	Intervention (I)/ Control (C)	Measurement tools and assessment timepoints	Effect size
Domar, 2005	Breast Mammography	I1: Listening to relaxation tape during screening mammography (N=50) I2: Listening to music tap during screening mammography (N=47) C: No tape (N=46)	- STAI - Likert anxiety score Timepoints: At recruitment and immediately after mammography.	Δ mean (SD) <u>STAI</u> Baseline: I1: 34.8 (9.7); I2: 33.6 (8.9); C: 33.2 (14.5), p-value 0.18 After mammography: I1: 30.4 (9.3); I2: 30.9 (10.0); C: 33.2 (13.3), p-value 0.78 <u>Likert anxiety score</u> After mammography: I1: 2.6 (1.9); I2: 3.2 (2.3); C: 2.8 (2.4), p-value 0.43
Ferrante, 2008	Breast Mammography	I: Patient navigator (N=55) C: No patient navigator (N=50)	<u>Measurement tools:</u> Zung Anxiety Self-Assessment Scale <u>Timepoints:</u> At enrolment and 1 month after final resolution (benign diagnosis or for cancer patients, after initiation of cancer treatment).	Δ mean (SD) Baseline: I: 38.7 (13.0); C: 36.6 (9.3), p-value 0.346 Follow-up: I: 30.2 (7.6); C: 42.8 (13.3), p-value<0.001 Δanxiety with time: I: −8.0 (10.6); C: 5.8 (14.0), p-value <0.001
Hersch, 2006	Breast Mammography	I: Decision aid including evidence-based information about important outcomes of breast screening compared with no screening (N=419) C: Control decision aid which omitted all overdetection-related content but was otherwise identical (N=419)	<u>Measurement tools:</u> - STAI - Structured questionnaire <u>Timepoints:</u> - Baseline interview 1-4 weeks after recruitment - Telephone interview 1-4 weeks after being sent decision aid	Δ mean (SD) <u>STAI</u>: I: 29·7; C: 29·6; Δ: 0·1, p-value 0·93 <u>Questionnaire</u> Worry about breast cancer (%) - Not worried at all: I: 42, C:32, Δ: 9·4 - A bit worried: I: 51, C:55, Δ: -3.9 - Quite worried or very worried: I: 7, C:13, Δ : -5.5 p-value 0.0026

Author, year	Cancer Test	Intervention (I)/ Control (C)	Measurement tools and assessment timepoints	Effect size	
Hilal, 2017	Cervix Colposcopy	I: Realtime video during colposcopy (N=111) C: No realtime video during colposcopy (N=105)	<u>Measurement tools:</u> - STAI - VAS <u>Timepoints:</u> - STAI: scores measured before (S1) and after (S2) colposcopy - VAS: anxiety during colposcopy	Δ median (IQR) <u>STAI</u> Before colposcopy (S1) After colposcopy (S2) ΔS(S1-S2) <u>VAS</u>	 I: 51 (42–62) C: 50 (41–61), p-value 0.73 I: 39 (33–50) C: 40 (33–48.5), p-value 0.80 I: -10.3 ± 11.3 C: -10.3 ± 11.0, p-value 0.50 I: 3 (1–5) C: 3 (1–5), p-value 0.61
Hilal, 2018	Cervix Colposcopy	I: Music during colposcopy (N=103) C: No music during colposcopy (N=102)	<u>Measurement tools:</u> - STAI - VAS <u>Timepoints:</u> STAI: scores measured before (S1) and after (S2) colposcopy VAS: anxiety during colposcopy	Δ median (IQR) <u>STAI</u> Before colposcopy (S1) After colposcopy (S2) ΔS(S1-S2) <u>VAS</u>	 I: 48 (42–59) C: 50 (41–59.25), p-value 0.91 I: 40 (33–47) C: 439 (32.75–46), p-value 0.92 I: -9.4 ± 10.8 C: -9.0 ± 10.6, p-value 0.40 I: 2 (1–5) C: 2 (1–6), p-value 0.28
Lang, 2006	Breast Large core needle biosy	I1: Self-hypnotic relaxation (N=78) I2: Empathic Attention (N=82) C: Standard of care (N=76)	<u>Measurement tools:</u> - Anxiety on VAS of 0–10 (t=0 to t=110 minutes) - STAI <u>Timepoints:</u> - Baseline anxiety - Self-rating anxiety every 10minutes in procedure room	Significant increase in anxiety in control No change in empathy group Significant decrease in hypnosis group	logit slope = 0.18, p < 0.001 logit slope = −0.04, p = 0.45 logit slope = −0.27, p < 0.001

Author, year	Cancer Test	Intervention (I)/ Control (C)	Measurement tools and assessment timepoints	Effect size
Shak, 2010	Colorectal Colonoscopy	I: Information aid including American Gastroenterological Association colonoscopy educational pamphlet along with prep instructions (N=51) C: Standard preparationinstructions only (N=55)	<u>Measurement tools:</u> STAI <u>Timepoints:</u> Immediately before colonoscopy	∆ mean <u>STAI</u> I: 40.54 C: 45.18, p-value 0.0146 <u>Medication usage</u> Midazolam (reduces anxiety) I: 2.35 C: 2.9, p-value 0.0444 Meperidine (reduces pain) I: 73.03 C: 76.81, p-value 0.374

†Abbreviations

Measurement tools include CRI - Coping Resources Inventory; COS-LC - Psychosocial consequences of lung cancer screening; HADS - Hospital Anxiety and Depression Scale; IES - Impact of Event Scale; Likert anxiety score; SF-12 – 12 item Short Form Health Survey; STAI - State-Trait Anxiety Inventory; VAS - *Visual Analogue Scale*; Zung Anxiety Self-Assessment Scale.

Other include LEEP – loop *electrosurgical excision* procedure; USS – ultrasonography; 'ns' refers to when authors did not report a p value

A total of 13 RCTs concerned with three cancers (breast, cervical, colorectal) were identified. The studies included screening (five studies) and diagnostic testing (eight studies). Interventions were assigned to five categories: use of information aids, music therapy, livestreaming of real-time videos during colposcopy, organisational factors (patient navigators, one-stop clinics), and pharmaceutical and homeopathic therapies. Psychological outcomes including anxiety, distress, depression, and worry were measured using validated tools such as the STAI, HADS, and IES questionnaires, author-designed questionnaires, or a combination of these. These outcomes were assessed at a single time point (at referral, before, during, or after receiving the intervention) or at two or more time points.

1. Use of information aids

Screening

One RCT in breast cancer testing reported on the effectiveness of information aids in the form of DVDs or printed materials. Hersch (Hersch et al., 2015) demonstrated a significant reduction in anxiety levels for women undergoing mammography with a significant reduction in breast cancer worry in the intervention arm.

Diagnosis

One RCT (Shaikh et al., 2010) showed a statistically significant reduction in STAI scores with the use of an education pamphlet for women undergoing colonoscopy, while de Bie (de Bie et al., 2011) did not find a clinically or statistically significant improvement in STAI scores in women attending for colposcopy.

2. Music therapy

Diagnosis

Four RCTs were identified associated with cervical (two), breast (one), and colorectal (one) testing.

Chlan (Chlan et al., 2000) demonstrated that music therapy was associated with a significant decrease in STAI scores in those attending for a flexible sigmoidoscopy.

Three RCTs (Chantawong and Charoenkwan, 2017, Domar et al., 2005, Hilal et al., 2018) did not demonstrate a significant effect of music therapy on anxiety levels in women undergoing cervical biopsies, colposcopy, or mammography, respectively.

3. Real-time videos during colposcopy

Diagnosis

The two RCTs (Camail et al., 2019, Hilal et al., 2018) which assessed the effectiveness of real-time videos in women attending for visualisation of the cervix following an abnormal smear result both failed to show a significant difference in STAI scores between both arms both before and after the procedure.

4. Organisational

Diagnosis

One RCT reporting on interventions during breast cancer testing (Ferrante et al., 2008) concluded that the presence of a patient navigator and an immediate communication of results may be helpful in lowering patient anxiety. One RCT (Dey et al., 2002) showed that one-stop clinics whereby women attending for breast cancer testing underwent investigations and received their results on the same day compared to women seen in the usual pathway was only beneficial in the short term (24 h) but not at follow-up after three weeks or three months.

5. Pharmacological and homeopathic therapies

Diagnosis

One RCT assessing homeopathy in women undergoing breast biopsies (Lang et al., 2006) noted a significant decline in anxiety with hypnosis and relaxation techniques following this intervention. Cruickshank (Cruickshank et al., 2005), on the other hand, did not find any significant change in the HADS scores with the self-

administration of an inhaled general anaesthetic (isoflurane) in women attending for colposcopy.

Conclusions for Question 2

Most RCTs were conducted in diagnostic populations for breast and cervical cancer. Of the five intervention categories, the use of information aids and organisational modifications such as the introduction of a patient navigator or one-stop clinics appeared to reduce anxiety. Homeopathic and complimentary therapies such as hypnosis may also be helpful. On the other hand, there was minimal evidence to support the use of music therapy or livestreaming of real-time videos during colposcopy. Overall, there is a paucity of evidence to support the majority of the interventions under consideration in this review for any cancer type or testing process.

Discussion

Summary of Findings

Some individual variables such as a real or perceived lack of knowledge of cancer testing, current or previous smoking history in lung and cervical cancer testing, and higher levels of trait anxiety as well as the invasive or intimate nature of some testing modalities (colonoscopy, flexible sigmoidoscopy, prostate needle biopsy, and colposcopy) have consistently been demonstrated to be associated with higher levels of fear, worry, embarrassment, and anxiety across various cancers (breast, colorectal, prostate, lung, and cervical cancers).

Our review suggested that cultural factors, language, and religious beliefs in women from non-white and immigrant communities may hinder attendance for cervical and breast cancer testing. However, the relevance of ethnicity as a risk factor for higher anxiety remains debatable in view of the variation in cancer types, testing modalities, study designs, and paucity of details with respect to the country of origin, refugee status, or ethnicity for non-native women. Similarly, the role of education remains unclear as the definitions used to report on different levels of education were non-uniform across the included studies. The relevance of age as a risk factor for anxiety was assessed in four SRs and 12 primary studies involving 3444 subjects. Its effect was unclear even within the same cancer. For instance, some BC studies showed that lower age was associated with high anxiety, while others showed no difference. This could be attributed to the heterogeneity in the age thresholds used to triage the subjects into ‘younger’ and ‘older’ categories across the included studies.

For interventions to mitigate the psychological associations of testing, our study appeared to confirm the effectiveness of informational aids which already constitute an integral part of patient care in a clinical setting across the U.K. Other, relatively novel organisational factors such as patient navigators or one-stop clinics seemed to play a role in mitigating anxiety levels. The evidence to support music therapy or real-time videos, which are an integral aspect of the majority of colposcopy clinics across the U.K., was less robust.

Strengths and Limitations of Review Methods

To our knowledge, this is the first review which addresses the harms of cancer testing and evaluates the effectiveness of interventions to mitigate their associations.

We conducted a comprehensive literature search and undertook quality assessment in duplicate. We acknowledge a limitation of our review methods is that screening, inclusion, and data extraction were conducted by a single author.

All the included SRs concerned with the psychological association of testing were narrative, and none of these offered a quantitative assessment of the results; it was therefore not appropriate to perform a meta-analysis. In addition, heterogeneity of cancer type, test, and interventions precluded meta-analysis. Heterogeneity of results even within similar populations and testing modalities may be explained by differences in outcome measurement. The outcome ‘psychological distress’ was used broadly and was often used interchangeably with anxiety, depression, stress, and distress across studies. The lack of a universal definition has resulted in the use of a broad spectrum of validated measurement tools including author-designed questionnaires. Finally, study quality was variable and a main limitation across the included primary studies in question was the non-identification of confounders, which undermines the validity of analyses.

The divergence in results across studies could thus be attributed to the lack of consistency pertaining to the heterogeneity across cancer types, measurement tools, definition of psychological distress, and time points at which psychological distress was assessed across studies.

With regard to question 2, most of the randomised controlled trials were conducted in patients attending for diagnostic rather than screening tests and therefore address the mismatch in the existing body of the literature, which is more well-researched in the context of screening tests. However, the interventions to

mitigate anxiety were primarily conducted for cervical, breast, and colorectal cancers, that is, cancers with an established screening programme in the U.K. The latter were overrepresented compared to cancers with a lower incidence but which are often lethal, such as ovarian, pancreatic, and lung cancers. Further research into methods to address individuals at risk of, or with symptoms suggestive of, these more lethal cancers would undoubtedly be more helpful to increase attendance for investigations, improve uptake of testing, and may perhaps improve survival through earlier diagnosis.

Finally, the most recent primary studies identified for both questions 1 and 2 were conducted in 2019. We acknowledge that the evidence is likely to have progressed since the completion of this review, thereby impacting on its currency.

Clinical Implications

The psychological benefit of cancer testing, namely, the reassurance afforded by an estimation of the patient's risk value for cancer following testing, has been described in the literature (Cantor et al., 2002). In addition to this, the mortality benefits of population-based screening for breast, lung, colorectal, and cervical cancers have been previously demonstrated (Duffy et al., 2020, de Koning et al., 2020, Shaukat et al., 2013, Landy et al., 2016). Although screening for ovarian cancer in asymptomatic average-risk women does not confer any survival benefit, further studies are underway to explore whether diagnostic testing of women who present to their doctors with suspicious symptoms could be associated with a survival benefit. To this end, there is an urgent need to investigate the psychological associations of cancer testing. Existing research is focused on screening for a select

number of cancers such as cervical, breast, and colorectal. However, certain fatal and deadly cancers such as ovarian and pancreatic cancers are underrepresented in the existing research portfolio. Evidence from our study suggests that the roles of some individual characteristics (age, ethnicity, educational attainments, employment status, and marital status) warrant further research to understand whether they are modifiers of the psychological associations of cancer testing. Assessment of the applicability of findings is further limited in view of the different screening and testing pathways employed in different countries. In terms of research methods, this area of research poses difficulties. For instance, it is difficult to blind participants and their assessors to interventions to mitigate anxiety in these testing contexts, especially if these involve non-concealable methods such as music therapy or real-time videos. Bias introduced by evaluation of outcome questionnaires may possibly be addressed to improve blinding of outcome measurement.

The result of our literature review suggests that some individual variables such as a real or perceived lack of knowledge of cancer testing, risk behaviours, higher levels of trait anxiety, and the invasive or intimate nature of some testing modalities have consistently been demonstrated to be associated with higher levels of fear, worry, embarrassment, and anxiety. These variables associated with testing encounters could be targeted for any interventions to mitigate the adverse psychological outcomes associated with cancer testing.

Our research demonstrates that modifiable (organisational) factors such as one-stop clinics and patient navigators for intervention evaluation may be beneficial in patients attending for cancer testing. With regard to interventions to mitigate anxiety, shifting towards one-stop clinics represents a potential route to expedite

diagnosis and may thereby be helpful to reduce the anxiety associated with prolonged waiting times. Continued use of information aids to educate patients about the cancer under review and the nature of and potential outcomes from associated investigations should be encouraged.

Conclusions

In summary, this literature search has identified some potential variables which may be associated with psychological morbidity in both screening and diagnostic cancer testing applications. Targeting certain patient groups and testing situations may offer a means to mitigate anxiety. Certain interventions may be helpful to mitigate the psychological morbidity associated with testing. A limited body of research suggests that one-stop clinics and patient navigators may be beneficial in patients attending for cancer testing. The contribution of some factors to anxiety in cancer testing and their specificity of effect are inconclusive and warrant further research in homogenous populations and testing contexts.

Using the results of the systematic review of the adverse psychological correlates of testing for cancer and the effectiveness of interventions to mitigate these to inform the analysis of primary data from ROCkeTS

The systematic review in Chapter 2 identified variables associated with psychological morbidity during testing for ovarian cancer (OC). Although there was a dearth of literature on the psychological impact of testing specifically for OC, common variables were identified across different test applications and a range of other target conditions.

Chapter 3 reports on an investigation of whether any of the variables identified in the literature review are associated with psychological morbidity in symptomatic women undergoing OC testing. In addition to variables identified from the literature associated with other types of cancer testing, it was hypothesised that previous or current gynaecological symptoms may be associated with psychological morbidity specifically in women referred for OC testing. By identifying the characteristics of women at a higher risk of psychological morbidity, these women could be targeted for additional support in order to reduce their risk of psychological morbidity. The prevalence of primary OC in women referred for OC testing is estimated, alongside a comparison of the prevalence of primary OC according to age and menopausal status.

CHAPTER 3

INVESTIGATING THE PSYCHOLOGICAL HARMS OF TESTING FOR OVARIAN CANCER IN SYMPTOMATIC WOMEN: A COHORT STUDY EMBEDDED IN THE MULTICENTRE, ROCKETS PROSPECTIVE DIAGNOSTIC STUDY

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Kwong FL, Kristunas C, Davenport C, Aggarwal R, Deeks J, Mallett S, Kehoe S, Timmerman D, Bourne T, Stobart H, Neal R, Menon U, Gentry-Maharaj A, Sturdy L, Ottridge R, Sundar S; ROCkeTS collaborators. Investigating harms of testing for ovarian cancer - psychological outcomes and cancer conversion rates in women with ymptoms of ovarian cancer: A cohort study embedded in the multicentre ROCkeTS prospective diagnostic study. BJOG. 2024 Mar 31. doi: 10.1111/1471-0528.17813. Epub ahead of print. PMID: 38556698.

Abstract

Objectives: To investigate psychological correlates in women referred with suspected ovarian cancer via the fast-track pathway, explore how anxiety and distress levels change 12 months post-testing and report cancer conversion rates by age and referral pathway.

Design: Single arm prospective cohort study

Setting: Multicentre. Secondary care including outpatient clinics and emergency admissions.

Participants: 2596 newly presenting symptomatic women with a raised CA125 level, abnormal imaging or both.

Methods: Women completed anxiety and distress questionnaires at recruitment and at 12 months for those who had not undergone surgery or a biopsy within 3 months of recruitment.

Main outcome measures: Anxiety and distress levels measured using STAI-6 and IES-r questionnaires. Ovarian cancer (OC) conversion rates by age, menopausal status and referral pathway.

Results: 1355/2596 (52.1%) and 1781/2596 (68.6%) experienced moderate-to-severe distress and anxiety at recruitment. Younger age and emergency presentations had higher distress levels. Clinical category for anxiety and distress remained unchanged/worsened in 76% at 12 months despite a non-cancer diagnosis. OC rates by age were 1.6% (95% CI 0.5 to 5.9) under 40 and 10.9 %

(95% CI 8.7 to 13.6) over 40 years. In women referred through fast-track pathways, 3.3% (95% CI 1.9 to 5.7) of pre- and 18.5% (95% CI 16.1 to 21.0) of postmenopausal women were diagnosed with OC.

Conclusions: Women undergoing diagnostic testing display severe anxiety and distress. Younger women are especially vulnerable and should be targeted for support. Women under 40 have low conversion rates and we advocate reducing testing in this group to reduce harms of testing.

Keywords: ovarian cancer, fast-track pathways, diagnosis, anxiety, depression, conversion rates

Tweetable abstract: Our study highlights the urgent need to review current practice to implement an age-stratified referral pathway for ovarian cancer, especially in women under 40 who are at higher risk of anxiety and distress but less likely to receive a diagnosis of ovarian cancer.

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Introduction

Ovarian cancer (OC), defined as ovarian, fallopian tube and primary peritoneal carcinomas, is the sixth most common cancer in women in the UK (CRUK). Disease stage at presentation is a robust predictor of survival. Most (95%) women diagnosed with Stage 1 OC survive their disease for 5 years compared to 15% of those diagnosed with Stage 4 disease. Screening has not shown a significant reduction in mortality (Buys et al., 2011, Jacobs et al., 2016) and national guidelines recommend that women with symptoms should undergo sequential testing with CA125 and ultrasound scan(NICE, 2011). Those with a raised CA125 level and abnormal imaging should be referred through a fast-track pathway to specialist gynaecologists within two weeks. Nearly 1 in 3 women with OC in the UK were diagnosed through this pathway in 2013 while 1 in 4 cases presented via emergency routes (Public-Health-England, 2016a). Unfortunately, the non-specific nature of symptoms together with the low sensitivity and specificity of CA125 result in a high rate of false positive referrals. In fact, only 4.0% (7978 of 198,783) of women who were urgently referred with a suspected gynaecological cancer ,including ovarian, in 2020-2021 had a confirmed diagnosis, that is with a cancer conversion rate of 4.0% (CRUK, 2022).

The harms of cancer testing including its therapeutic, financial, legal and psychosocial implications are well-described (Petticrew et al., 2000). In certain cancer subtypes namely breast, lung, colorectal and cervical (Duffy et al., 2020, de Koning et al., 2020, Shaukat et al., 2013, Landy et al., 2016) where population-based testing has demonstrated a clear mortality benefit, the survival benefit following an early diagnosis undoubtedly outweighs its psychological harms. For OC however, screening has not been shown to confer any survival advantage and the benefits of

diagnostic testing through the fast-track pathway remain unclear. Harms of OC testing should thus be carefully considered especially in premenopausal women where the incidence of an ovarian cyst being cancerous is 1 in 1000 compared to 3:1000 in those over 50 (RCOG, 2011).

Our previous review (Kwong et al., 2023) highlighted that most studies reporting on the psychological harms of OC testing were conducted in women attending for screening and not diagnostic testing. More recent studies have described the patient experience following a referral via the fast-track pathway for OC (Rowlands et al., 2022, Haste et al., 2020, Jefferson et al., 2019, Lof et al., 2022). All these studies were qualitative, with a sample size ranging from 24 to 417 participants and patient experiences evaluated at a single time point. In this study, we report on anxiety and distress levels at two time points in over 2500 participants, identify which variables correlated with psychological harms, and analyse the OC conversion rate by age, menopausal status and referral pathways.

Methodology

Patient and public involvement in the research

The patient information leaflet for the ROCkeTS study was reviewed by four research advocates from the Target Ovarian Cancer charity. A patient representative sat on the project management group and regularly advised on study conduct.

Variables Under Investigation

We had previously performed a systematic review (Kwong et al., 2023) to identify which patient and/or organisational factors may modify the psychological impact of cancer

testing. Based on clinical experience, we also hypothesised that women with risk factors for OC or with existing or previous gynaecological complaints may be self-aware about their higher risk of OC from publicly available information platforms, such as charity leaflets (Marsden, 2022, D et al., 2019, Sallam et al., 2013).

Study protocol

ROCkeTS is a single-arm prospective observational diagnostic test accuracy study whereby all participants donate a blood sample for Risk of Malignancy Algorithm (ROMA) biomarker testing (Moore et al., 2011) which predicts the likelihood of an ovarian malignancy based on the CA125 and HE4 results and the menopausal status, and undergo an ultrasound scan scored using International Ovarian Tumour Analysis terminology (Timmerman et al., 2000). Participants completed a series of questionnaires at various time points (S1 Fig). Women were recruited from 24 hospitals across the UK in outpatient settings (fast-track pathway, non-urgent outpatient referrals) and following emergency admissions. All participants were given an information leaflet and had their eligibility confirmed by a doctor. Written informed consent was obtained from all participants. Patient data was collected on standard proformas. The outcome of testing was ascertained by histology from biopsy or surgery if these were performed within 3 months of referral, or at clinical follow up at 12 months using a wellbeing questionnaire for those who had not undergone a biopsy or surgery. Results of the diagnostic test accuracy of biomarker and ultrasound testing are awaited.

Participants

Women between 16 and 90 years who had been referred to secondary care with symptoms and either a raised CA125 level, an abnormal scan, or both were included. Pregnant women or those with a previous history of OC were excluded.

Postmenopausal recruitment commenced June 2015 and completed in 2018. Premenopausal recruitment commenced June 2015 and was completed in March 2023. After March 2018 (protocol version 7.0), premenopausal women were only eligible if they were scheduled to undergo a procedure (surgery or biopsy) due to very low rates of OC in premenopausal recruits. Only women recruited prior to the protocol change were included in the calculation of the OC conversion rate in premenopausal women. This was to reduce selection bias from including premenopausal women undergoing surgery for a suspicious ovarian mass as these women would automatically be classified as being at higher risk of OC than those referred for symptoms and abnormal testing alone.1124 women, including 548 premenopausal and 576 postmenopausal subjects had been recruited prior to protocol change.

Timelines

Recruitment: Women completed a baseline questionnaire at recruitment. This usually coincides to a referral by their GP to see a gynaecologist in hospital.

3 months: Most women would have been triaged into low or high risk of OC using the current standard of triage in the UK that is the Risk of Malignancy Index (RMI) at three months (Jacobs et al., 1990). Women in the high risk category undergo investigations (biopsies) or interventions (surgery) to attain a histological diagnosis.

12 months: Women without a histological diagnosis (no biopsy or surgery at three months) were followed up at 12 months. This cohort represents women who were positive for initial tests (CA125, symptoms indicating possible OC, abnormal imaging)

but in whom an OC diagnosis was not confirmed following diagnostic testing or those who were triaged as ‘low risk’ by the RMI tool.

Study Measures

All participants completed the Impact of Events Scale – Revised (IES-r) and a six-item short form of the State Trait Anxiety Inventory (STAI-6) questionnaires at recruitment. For women who had not undergone surgery or biopsy within 3 months of recruitment, questionnaires were administered again at 12 months (S1 Fig). When comparing the trajectory in anxiety and distress levels at recruitment and after 12 months, we excluded all participants diagnosed with OC or other cancers at 12 months. These two questionnaires have previously been used in cancer screening studies and are validated tools to measure anxiety and distress.

Anxiety

The STAI is a self-assessment questionnaire consisting of 20 items (Spielberger CD, 1983). Each statement is rated on a four point scale. Scores range from 20 to 80 with lower scores reflecting milder degrees of anxiety. Scores can be grouped into three clinical categories: ‘no or low anxiety’ (20-37), ‘moderate anxiety’ (38-44), and ‘high anxiety’ (45-80). The shortened STAI-6 used in ROCkeTS is an abbreviated six-item short form of the STAI questionnaire giving a score range from 6 to 24. To create scores and categories compatible with the original STAI scores, the score for each participant was calculated by dividing their score by 6 and multiplying by 20 as per literature (Graff et al., 2019). This

questionnaire was selected as it is quicker for participants to complete in an outpatient setting.

Distress

The IES-r is a set of 22 five-point Likert scale questions to measure distress and yields a total score of 0 to 88 (Weiss DS, 1997). Using this tool, participants report on the effects of intrusive thoughts related to an event (their referral for OC testing) and their efforts to avoid any recollection of this event. Scores on the IES-r are used to define three clinical categories: ‘Post traumatic stress disorder - PTSD is a clinical concern’ (24 -32), ‘probable PTSD’ (33 - 36) and ‘severe enough to suppress the immune system; effects may persist 10 years following the event’ (37 or more).

Statistical analysis

The aim of this study was to compare anxiety and distress levels at recruitment for all participants and at 12 months post-testing in women not diagnosed with OC. We also calculated the OC conversion rate in the referred women. Women were grouped as postmenopausal if they had not had a period for over 12 months. In women who had been amenorrhoeic for over 12 months for reasons such as contraception or hysterectomy, the menopausal status was assigned according to their age; women up to the age of 50 were considered premenopausal while those aged 51 and above were considered postmenopausal. Only women recruited prior to the implementation of protocol version 7.0 were included in the analysis of premenopausal women for this study. This manuscript includes the majority of recruits to ROCkeTS. All analyses were performed using Stata version 16.

Analysis of psychological questionnaires

Categorical data was presented using frequencies and percentages. Scores from the STAI and IES-r questionnaires were treated as continuous variables. The normality of their distributions was assessed. Outcome measures which followed a normal distribution were presented as mean and standard deviation and median and interquartile ranges for those with a non-normal distribution. The association between STAI and IES-r scores with explanatory variables was explored using the appropriate parametric or non-parametric tests (Wilcoxon Rank-Sum and Kruskal-Wallis tests). Results with a p-value<0.05 were considered statistically significant.

Analysis of cancer conversion rates

OC conversion rate as described by the National Cancer Intelligence Network (NCIN) refers to the percentage of women diagnosed with OC following an urgent referral for suspected OC. We calculated the OC conversion rate in all recruited postmenopausal women and in the subset of premenopausal women recruited prior to the protocol change which limited recruitment of premenopausal women to pre-surgical patients only.

Results

2596 participants were included in the analysis. 85.1% completed the STAI-6 (2208/2596) and 85.6% completed the IES-r questionnaires (2222/2596) at recruitment (S2 Fig). 31.8% (825/2596) women had not had a biopsy or undergone surgery at three months and received a follow-up questionnaire at 12 months. 56.6%

and 57.3% of these completed the STAI-6 (467/825) and IES-r (473/825) questionnaires (S2 Fig).

The sociodemographic characteristics of all participants are presented in Table 1. The median and interquartile range for age was 53(43-65) years and 55.2% (1432/2596) were postmenopausal. 52.3% (1358/2596) were employed and 45.6% (1185/2596) had at least secondary school level qualifications. 62.6% (1624/2596) lived with a partner. 92.1% (2391/2596) of participants were White.

Table 1. Sociodemographic characteristics of all participants

Characteristic	**Number (%) * N=2596**
Age Median (interquartile range), years	53 (43-65)
Postmenopausal	
Yes	1432 (55)
No	1164 (45)
Living situation	
Lives alone	875 (34)
Lives with partner	1624 (62)
Unknown	97(4)
Employment status	
Employed	1202 (46)
Self-employed	156 (6)
Retired	790 (30)
Unemployed	169 (7)
Student or other	186 (7)
Unknown	93 (4)
Highest level of education	
No qualifications	504 (19)
At least secondary school level	1185 (45)
At least tertiary level	598 (23)
Other	209 (8)
Unknown	100 (4)
Ethnic group	
White	2311 (89)
Non-White	192 (7)
Unknown	93 (4)

*unless otherwise stated

The clinical characteristics and outcomes for all women is shown in Table 2. 67.0% (1741/2596) presented via the fast-track pathway, 17.8% (463/2596) were referred by Cancer Units and other specialties, 8.8% (229/2596) via routine GP referrals and only 6.4% (163/2596) via the emergency route. 94.5% (2454/2596) of all participants were of good performance status (0 and 1) and 43.0% (1117/2596) were current or ex-smokers. 38.2% (991/2596) completed questions about their gynaecological history. 6.0% (156/2596) had a previous history of subfertility, 8.4% (217/2596) reported postmenopausal bleeding, 12.4% (322/2596) had used contraception, 16.7% (436/2596) used hormone replacement therapy, and 21.3% (553/2596) had experienced a change in nature of their periods. 10 women who were initially triaged as being at low risk of OC at three months were eventually diagnosed with primary OC at 12 months. 30/2596 women (1.2%) were diagnosed with non-OC at 12 months and breast cancer was the most common non-OC diagnosis.

Table 2. Clinical characteristics and outcomes of participants

Characteristic	**N (%)** **N=2596**
Route of presentation	
Accident and Emergency	163 (6)
Fast-track pathway	1741 (67)
Referral from Cancer Unit or cross specialty referrals	463 (18)
Routine GP referral	229 (9)
WHO Performance Status	
0	2178 (83)
1	276 (11)
2	65 (3)
3	34 (1)
4	2 (<1)
Unknown	41 (2)

Characteristic	N (%) N=2596
Ever smoked	
Yes	1117 (43)
No	1384 (53)
Unknown	95 (4)
History of subfertility	
Yes	156 (6)
No	839 (32)
Unknown	1601 (62)
Change in nature of periods	
Yes	553 (21)
No	442 (17)
Unknown	1601 (62)
Past or current use of contraception	
Yes	322 (13)
No	669 (26)
Unknown	1605 (62)
History of postmenopausal bleeding	
Yes	217 (8)
No	742 (29)
Unknown	1637 (63)
Past or current use of HRT	
Yes	436 (17)
No	1039 (40)
Unknown	1121 (43)
<u>Clinical outcomes</u>	
Diagnosed with primary OC	251 (10)
Diagnosed with non-OC at 12 months	30 (1.2) n(% of cases of non-OC)
Breast	7 (23)
Uterine	5 (17)
Bowel	5 (17)
Lymphoma	3 (10)
Lung	3 (10)
Renal	3 (10)
Gastric	2 (7)
Pancreatic	1 (3)
Skin	1 (3)

At recruitment, distress levels were severe in 53.3% (1185/2222), moderate in 7.7% (170/2222) and mild in 39.0% (867/2222), while anxiety levels were severe in 48.5% (1071/2208), moderate in 32.2% (710/2208), and mild in 19.3% (427/2208). We compared the median STAI and IES-r scores at recruitment between women who completed the 12-month questionnaire and those did not. As the 12-month questionnaire was only completed by women without a histological diagnosis, the subgroup of women who completed the questionnaires at 12 months comprised only those with a false positive (FP) result at recruitment. Women with a histological diagnosis confirming OC (TP) or a benign pathology (FP) were not included at 12 months and were therefore not sent a follow up questionnaire in line with the ROCkeTS protocol. Similarly, ROCkeTS did not include a cohort of false negative (FN) patients as all the participants were symptomatic and had an abnormal CA125 and/or imaging at recruitment. There was no clinical or statistically significant difference in median STAI scores among responders and non-responders (43 (40-50) vs 43 (40-50), p=0.470). Similarly, we did not find any significant difference in the median IES-r scores, that is 34 (25-53) vs 34 (24-48), p=0.323.

An analysis of the factors associated with anxiety or distress at recruitment is illustrated in Table 3.

Table 3. Analysis of factors associated with anxiety or distress at recruitment.

	Responses n (%)	**STAI score** Median (IQR)	**IES-r score** Median (IQR)
Age - Under 40 - Over 40	 444 (18) 2151 (82)	p=0.172 43 (40-50) 43 (40-50)	p=0.788 44 (30-63) 40 (28-60)
Age* - Under 50 - Over 50	 989 (38) 1606 (62)	p=0.823 43 (40-50) 43 (40-50)	**p<0.001** 44 (30-63) 40 (28-60)

	Responses n (%)	**STAI score** Median (IQR)	**IES-r score** Median (IQR)
Marital status**		p=0.710	p=0.690
- Living alone	875 (35)	43 (40-50)	42 (29-60)
- Living together	1624 (65)	43 (40-50)	41 (29-63)
- Other	2 (2)	48 (43-53)	39 (28-49)
Employment status**		p=0.079	**p<0.001**
- Employed fulltime or part-time	1202 (48)	43 (40-50)	44 (30-63)
- Self employed	156 (6)	43 (40-50)	41 (28-59)
- Retired	790 (32)	43 (40-50)	36 (27-55)
- Unemployed	169 (6)	47 (40-50)	43 (29-72)
- Student	186 (8)	47 (40-50)	42 (28-64)
Educational level**		p=0.211	**p=0.001**
- No qualifications	504 (20)	47 (40-50)	38 (27-59)
- At least secondary level	1185 (47)	43 (40-50)	42 (29-63)
- At least tertiary level	598 (24)	43 (40-50)	44 (31-62)
- Other	209 (9)	43 (40-50)	38 (26-59)
Ethnicity*		p=0.196	p=0.266
- Non-White	192 (8)	47 (40-50)	42 (29-70)
- White	2311 (92)	43 (40-50)	41 (29-61)
Ever smoked*		p=0.854	p=**0.027**
- No	1384 (55)	43 (40-50)	41 (28-60)
- Yes	1117 (45)	43 (40-50)	42 (30-63)
Route of presentation**		p=0.614	**p<0.001**
- Accident and emergency	163 (6)	47 (40-50)	45 (30-65)
- Rapid Access Clinic referrals	1741 (67)	43 (40-50)	43 (30-63)
- Cancer unit or other specialties	463 (18)	43 (40-50)	39 (27-59)
- Routine GP referral	229 (9)	43 (40-50)	33 (26-53)
Performance status**		p=0.636	p=0.606
- 0	2178 (85)	43 (40-50)	42 (29-62)
- 1	276 (11)	47 (40-50)	40 (29-60)
- 2	65 (3)	43 (40-50)	39 (29-62)
- 3	34 (1)	43 (40-50)	35 (28-48)
- 4	2 (<1)	45 (40-50)	42 (38-46)
History of subfertility*		p=0.553	p=0.884
- No	839 (84)	43 (40-50)	45 (31-63)
- Yes	156 (16)	43 (40-50)	47 (30-60)
History of ovarian stimulation for subfertility*			
- No		p=0.099	p=0.841
- Yes	927 (93)	43 (40-50)	45 (31-63)
	65 (7)	47 (40-50)	48 (32-62)

	Responses n (%)	**STAI score** Median (IQR)	**IES-r score** Median (IQR)
Change in nature of periods*		p=0.249	**p=0.015**
- No	442 (44)	43 (40-50)	44 (29-61)
- Yes	553 (56)	43 (40-50)	47 (32-64)
Use of contraception*		p=0.959	p=0.301
- No	669 (67)	43 (40-50)	46 (31-64)
- Yes	332 (33)	43 (40-50)	44 (30-61)
Postmenopausal bleeding*		p=0.498	p=0.885
- No	742 (77)	47 (40-50)	38 (28-60)
- Yes	217 (23)	43 (40-50)	38 (28-60)
Current of previous use of HRT*		p=0.080	p=0.167
- No	1039 (70)	47 (40-50)	38 (28-59)
- Yes	436 (30)	43 (40-50)	40 (29-61)
Number of pregnancies**		p=0.780	p=0.147
- 0	97 (5)	43 (40-50)	43 (32-65)
- 1 to 4	1645 (91)	43 (40-50)	41 (29-61)
- 5 or more	61 (4)	47 (40-50)	34 (24-66)

*The Wilcoxon Rank-Sum test was used to calculate the p-value

**The Kruskall-Wallis test was used to calculate the p-value

Age and other clinico-demographic variables

Women under 50 displayed a higher median (interquartile range) IES-r score compared to those over 50 (44(30-63) versus 40 (28-60), p<0.00). Being retired was a protective factor for distress as these participants reported ‘moderate distress’ (36 (27-55)) compared to ‘severe distress’ in the rest of the cohort. There was a positive correlation between the level of education and IES-r scores at recruitment. This did not translate to a change in the clinical categories of distress levels however, as the median IES-r scores were over 37 (i.e. ‘severe’ distress) for women from each educational level categories. Women who described a change in their periods scored higher on the IES-r questionnaire. There was no correlation between distress levels and clinico-demographic factors (marital status, ethnicity, performance status) or other gynaecological variables (history of subfertility, history of ovarian stimulation,

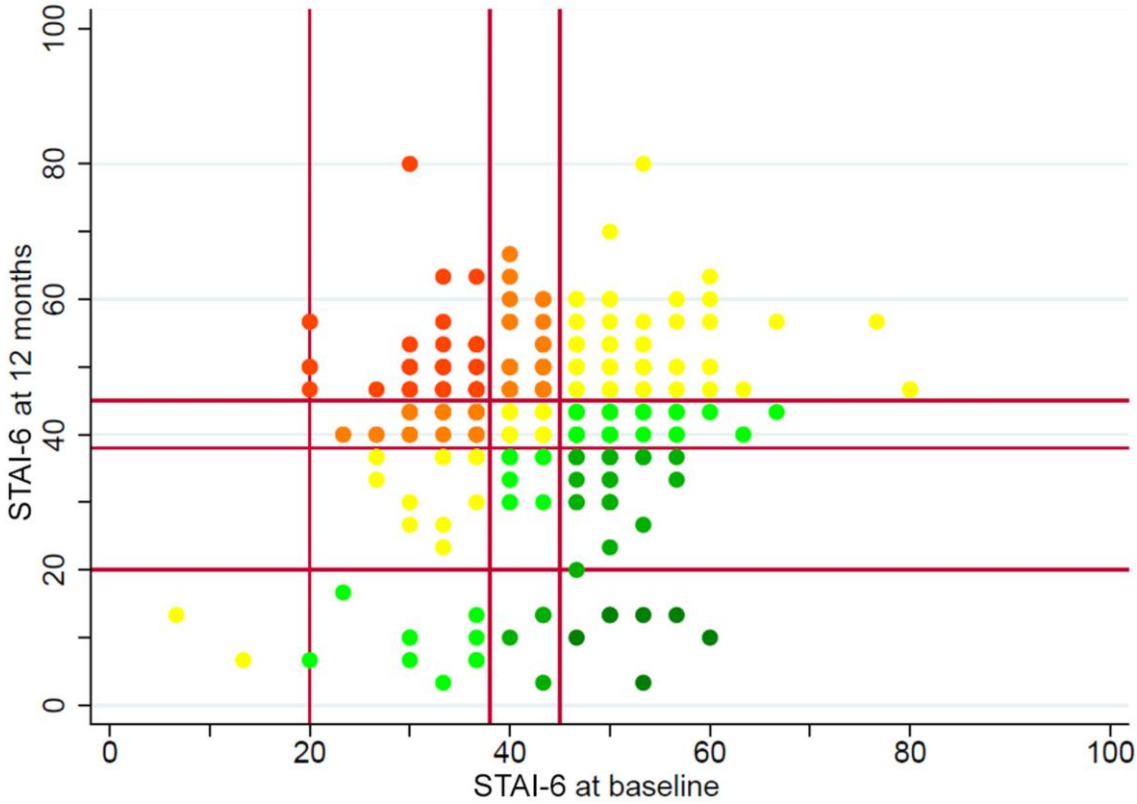
use of contraception, postmenopausal bleeding, use of HRT and parity). There was no clinical or statistical correlation between any of the variables considered and anxiety levels at recruitment.

Route of referral

Routine GP referrals were associated with moderate levels of distress at recruitment while emergency presentations resulted in the highest distress levels, (33 (26-53) versus 45 (30-65), $p<0.00$).

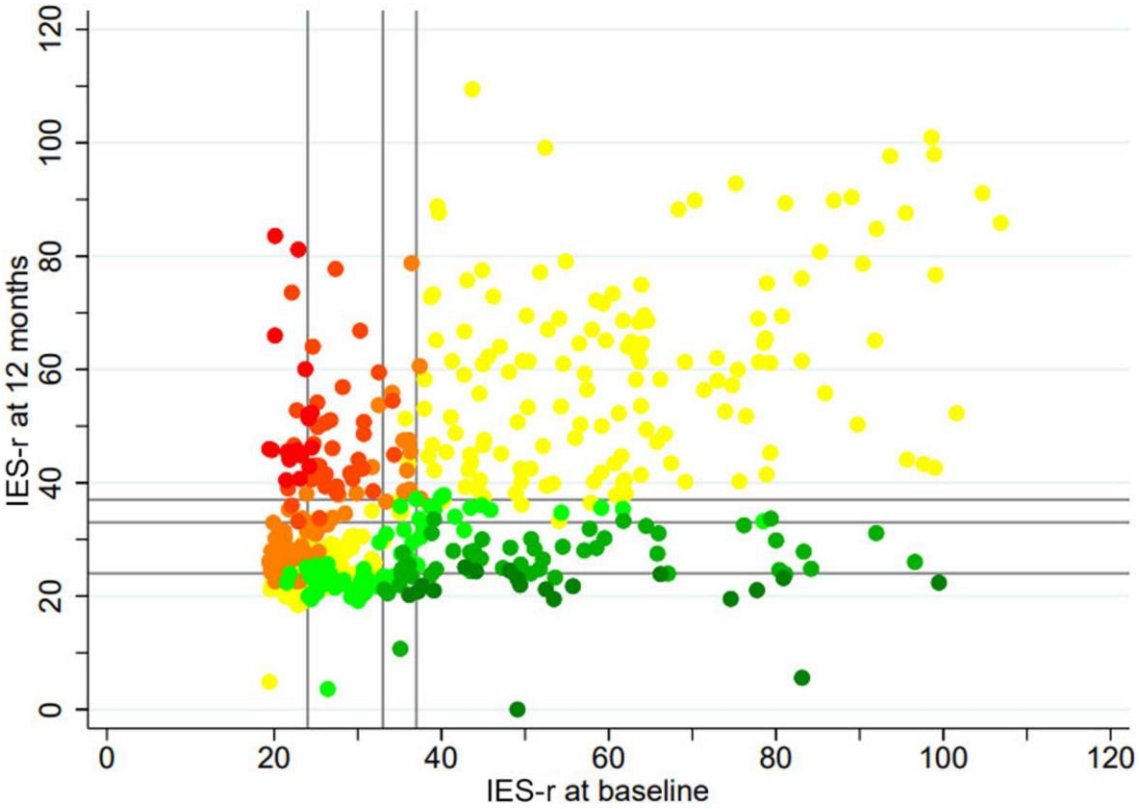
There was no change in the clinical category for anxiety levels in 46% of respondents, while 30% experienced increased anxiety and 24% had improved by 12 months (Fig 1 and S1 Table). There was no change in the clinical category for distress levels in 66% of respondents, while 20% reported an improvement and 14% experienced more severe distress at 12 months (Fig 2 and S2 Table).

Fig1. Heat map to illustrate change in STAI-6 scores at recruitment and at the 12 month follow-up among 467 respondents.



Red dots represent subjects in whom distress levels became more severe by three categories, yellow in those in whom clinical anxiety or distress category remained unchanged and dark green in those in whom the anxiety or distress levels improved by three categories.

Fig 2. Heat map to illustrate change in IES-r scores at recruitment and at the 12 month follow-up among 473 respondents.



Red dots represent subjects in whom distress levels became more severe by three categories, yellow in those in whom clinical anxiety or distress category remained unchanged and dark green in those in whom the anxiety or distress levels improved by three categories.

Overall, the true positive diagnosis rate of OC in premenopausal women was 19/548 (3.5%) compared to 232/1432 (16.2%) for postmenopausal women. Of those referred via the fast-track pathway, 12/363 (3.3%, 95% CI 2.2 to 5.4) were diagnosed with primary OC in premenopausal compared to 181/979 (18.5%, 95% CI 14.4 to 18.2) in the postmenopausal subjects at 12 months (Table 4).

Table 4. OC conversion rate per mode of presentation in premenopausal women prior to protocol change[&] and all post-menopausal women

	Premenopausal			Postmenopausal		
	n*	N**	% (95% CI)	n*	N**	% (95% CI)
Accident and Emergency	3	32	9.4 (3.2, 24.2)	11	67	16.4 (9.4, 27.0)
Fast-track pathway	12	363	3.3 (1.9, 5.7)	181	979	18.5 (16.1, 21.0)
Cancer Unit or cross-specialties	2	77	2.6 (0.7, 9.0)	36	290	12.4 (9.1, 16.7)
Routine GP referral	2	76	2.6 (0.7, 9.1)	4	96	4.2 (1.6, 10.2)
Overall	19	548	3.5 (2.2, 5.4)	232	1432	16.2 (14.4, 18.2)

*n represents number of women with a true diagnosis of OC
**N represents number of women referred via a mode of presentation
% represents the proportion of women presenting via a mode of presentation and who were identified with a true diagnosis of OC
& - In pre-menopausal women, protocol for recruitment was altered in 2018 to only include women undergoing surgery or biopsy due to the very low rate of cancer in recruited participants.

Tabulation of OC rates showed that no women referred under the age of 29 was diagnosed with OC (S3 Table). Only 1.6% of women under 40 (irrespective of menopausal status) were diagnosed with OC.

Discussion

Main Findings

This large, multicentre, prospective study investigated the psychological impact of diagnostic testing for suspected OC. Most women experience severe distress and anxiety at recruitment and these remain unchanged/worsened in the majority at 12 months, even in the absence of an OC diagnosis. Our results showed that women aged 50 years and over reported lower distress compared to those under 50 years. Women who presented via the emergency pathway reported the highest level of distress. The OC conversion rate was at least four times higher in postmenopausal compared to premenopausal women. OC conversion rate varied

substantially by age, with very low rates in women under 40 (1.6%, 95% CI 0.5 to 5.9) compared to those over 40 (10.9 %, 95% CI 8.7 to 13.6). Furthermore, there was a positive correlation between cancer conversion rates, and by extension the mode of presentation, and distress levels, with women recruited via the fast-track pathway displaying the highest level of distress compared to those diagnosed with OC following a routine GP referral where the OC conversion rate was the lowest. In summary, younger women display higher levels of distress but are much less likely to receive a diagnosis of OC. Their persistent high anxiety levels despite not being diagnosed with OC suggest that they mandate additional support. However, it is important to acknowledge that some women aged under 40 may still be at high risk of OC because of factors other than age and further investigation is justified in this cohort. To the best of our knowledge, our study is the first multicentre prospective study including outcomes for women referred under the fast-track pathway.

Interpretation, in light of other evidence

Our results support findings from screening studies (Andersen et al., 2007, Wardle et al., 1993, Andrykowski, 2017, Andrykowski et al., 2004, Taylor et al., 2004, Barrett et al., 2014, Brain et al., 2012) which described a significant increase in OC-specific worry and distress even in women without a cancer diagnosis. A recent study by Lof *et al* (Lof et al., 2022) explored women's experience of a referral and workup for surgery for an ovarian mass. Their results demonstrated that 57% of recruits experienced clinically significant cancer-specific distress levels preoperatively when the histology was unclear. 99% of women who were identified with a benign ovarian mass were satisfied with the diagnostic pathway. The authors therefore concluded that patients were receptive to a referral for investigations and treatment, even if their

estimated risk of OC was low. Our study differs from Lof *et al* for a number of reasons: our participants were not restricted to those scheduled for surgery only. We also compared anxiety and distress levels at two time points to accurately assess the detrimental effects of a referral for possible OC, especially in women with a false positive result.

Our results illustrate that there is a clear association between a referral for testing for OC and high anxiety and distress levels which remain elevated at 12 months even in the absence of an OC diagnosis. National statistics figures (Office-of-National-Statistics, 2022) demonstrate that one in three adults experience high anxiety levels and 30% of the population experiences some form of distress with 6.2% reporting 'high' levels (Office-of-National-Statistics, 2022). Approximately one in two women recruited to our study reported high levels of anxiety and distress at recruitment, i.e., higher than UK baseline rates. It is possible that our participants represent the 'worried-well' that is women who perceive themselves as being more likely to develop OC, have a higher awareness of the manifestations of OC and therefore present to their GPs with these symptoms. These are usually educated patients who are often proficient at information seeking (Myrick and Willoughby, 2019, Spence, 2016).

Anxiety levels remained unchanged or worsened in 76% of women despite the absence of an OC diagnosis at 12 months. This could be explained by a higher level of trait anxiety as suggested by Wiggins et al (Wiggins et al., 2019). The authors measured OC-specific distress levels at various time points (baseline, 1 month, 4 months) in 373 women recalled following a false positive transvaginal ultrasound scan (TVS) result. Their results demonstrated that although distress levels declined

in women in with high baseline levels, these remained elevated at four months. A multivariate analysis identified a family history of OC, a monitoring coping style and weaker optimism as possible predisposing factors. Our study further demonstrates a negative correlation between age and distress levels. Lower anxiety levels in older women have also been noted in UKCTOCS (Barrett et al., 2014).

Strengths And Limitations

ROCkeTs is a prospective study and our analysis includes a sample of over 2500 women recruited from 24 sites. For patients with missing data, additional information was procured by the research nurses by accessing the medical records or by contacting their GPs. Our protocol was also carefully designed to exclude all those with a diagnosis of cancer at 12 months as part of our pre-planned analysis plan. Our inclusion criteria were restricted to newly presenting patients only to ensure that our cohort rigorously adhered to the criteria for OC testing. Finally, this is the first multicentre study which explores the OC conversion rate in premenopausal and postmenopausal women referred to fast-track clinics. Our finding of differential OC rates by age is consistent with the epidemiology of OC with a peak incidence in the 70's age group (CRUK).

One of the limitations of our study is that the majority of responders were White females. We concede that women who declined or withdrew consent may either have been overwhelmed or dissuaded from taking part following language, cultural or socioeconomic obstacles. Our results may therefore not be representative of some of the most vulnerable subgroups of women. However, we did not find a significant difference in anxiety and distress levels at recruitment among responders and non-responders at 12 months. This suggests that factors other than higher levels of pre-existing anxiety and distress should be considered to account for the loss to

follow up rate in this study. Follow-up data was only available for 60% of women without a diagnosis of cancer at 12 months and may not be representative of all women in this category.

It was not possible to infer causality or demonstrate whether abnormal preliminary results and a referral to hospital for further testing generate higher anxiety and distress. Firstly, a comparison of the anxiety and distress levels among women with a true negative result (symptomatic but normal results) and those with a false positive result (symptomatic and abnormal results) would be necessary to explore to what degree the presence of symptoms and a fear of cancer contribute to anxiety and distress. Secondly, we do not have a measure of baseline anxiety and distress levels in women in the community. It was therefore not possible to demonstrate a temporal relationship between a referral for OC testing and a change in anxiety and distress levels.

Implications for Practice and Future Research

Our results also accentuate an urgent need to review current practice to implement an age-stratified referral pathway. In this study, the prevalence of OC in women under 50 did not reach the 3% threshold advocated by NICE. Funston et al (Funston et al., 2020) demonstrated that a higher CA125 threshold of 89U/ml is necessary to attain a 3% probability in women under 50, compared to 39 U/mL for those 50 and above and proposed that clinicians should be more selective (risk in excess of 3% calculated from their age and CA125) in referring patients for further investigations. Alternatively, women could be counselled about their individualised risk of OC and a plan of care mutually agreed. Current international guidelines do not place emphasis on OC testing by age or menopausal status (Redman et al., 2011, SIGN, 2018, ACOG-SGO, 2017). Further quantitative

research accompanied by qualitative research is warranted to evaluate the effectiveness and patient experience of any interventions to mitigate the adverse psychological impact of testing in this population.

Efforts should focus on diagnostic pathways such as one-stop clinics to ensure a rapid diagnosis and address the fragmentation across multiple appointments whilst improving psychological outcomes (Singh et al., 2017, Gray, 1997). There is evidence (Gray, 1997, Dey et al., 2002) to support its use in reducing anxiety in breast cancer testing. Future research focusing on low-risk women e.g., under 40, is essential to investigate how anxiety and distress levels compare among women referred via different routes, explore what is needed/wanted by women to improve their experience of the OC testing pathway, and evaluate whether the fast-track pathway contributes to higher psychological morbidity in this cohort, or whether it mitigates these by reducing waiting times.

Conclusion

This study demonstrates that women under the age of 50 years and those who were referred via the emergency route are at high risk of distress. Patients referred to gynaecology clinics with an abnormal CA125 level and/ or ultrasound tests for OC testing have high persistent levels of anxiety and distress irrespective of the final histological diagnosis. Efforts should focus on improving counselling and support in young women, especially under the age of 40 as the prevalence of cancer in these women is 1.6% which is below the NICE recommended threshold of 3% for cancer testing. Considering the increase in anxiety and distress demonstrated by our study in

women less than 50 years, combined with the prevalence of OC in women under 40 years, we would suggest that the harms of testing for OC in women under 40 outweigh the benefits.

Acknowledgements

We wish to thank all the women who consented to participate in this study and the ROCkeTS collaborators.

Data sharing and data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Disclosure of interest

None

Contribution to authorship

SS, HS, CD, SM, SK and JD conceptualised and designed the study and helped with statistics for the study, with input from the study coordinating team (LD, RO). RN, DT, TB, AG-M and UM provided critical input into study design and helped in writing of the manuscript. FLK and CK did the statistical analysis with support from SM and RA. FLK, CD, CK and SS prepared the figures and tables. FLK, CD, CK and SS interpreted data and drafted the report. All authors critically reviewed the report and approved it before submission. The corresponding author attests that all listed

authors meet authorship criteria and that no others meeting the criteria have been omitted.

Details of ethics approval

This study has received ethics permission from the NHS West Midlands REC (Ref14/WM/1241) and has no specific safety considerations. Outputs will be disseminated through open access publications, on the website http://www.birmingham.ac.uk/ROCKETS.

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What are the surgical outcomes of the fast-track pathway for women diagnosed with the most lethal form of ovarian cancer, that is the high grade serous subtype?

In Chapter 3, the psychological impact of ovarian cancer (OC) testing on symptomatic women referred from the community was described. The majority of women were recruited via the fast-track pathway which was implemented in the UK in 2011. The findings presented in Chapter 3 suggest that the fast track OC testing pathway has the potential to have a negative psychological impact on women. It is therefore important to understand whether current practice, with the potential to cause psychological morbidity, is providing clinical benefit.

High grade serous OC is directly responsible for 90% of mortality in women diagnosed with this disease. This was the focus of the investigation presented in the following chapter. Performance status, disease stage, disease distribution/extent of disease and complete cytoreduction rates are prognosticators of OC. The following chapter reports an analysis of the ROCkeTS cohort to investigate the impact of symptom-triggered testing via the fast-track pathway on these clinical outcomes. The results from the ROCkeTS cohort are compared to previous studies, namely the UKCTOCS and DOvE study, to assess whether the fast-track pathway contributes to superior surgical outcomes.

CHAPTER 4

SYMPTOM-TRIGGERED TESTING IMPROVES THE DETECTION OF EARLY STAGE, LOW VOLUME HIGH GRADE SEROUS OVARIAN CANCER AT GOOD PERFORMANCE STATUS AND LEADS TO HIGH COMPLETE CYTOREDUCTION RATES.

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A version of this manuscript has been accepted for publication in the *International Journal of Gynecological Cancer*

Abstract

Objective: Symptom-triggered testing for ovarian cancer was introduced to the UK whereby symptomatic women undergo an ultrasound scan and serum CA125 and are referred to hospital within two weeks if these are abnormal. The potential value of symptom-triggered testing in the detection of early-stage disease or low tumour burden remains unclear in women with high grade serous ovarian cancer. In this descriptive study, we report on the FIGO stage, disease distribution and complete cytoreduction rates in women presenting via the fast-track pathway and who were diagnosed with high grade serous ovarian cancer.

Methods: We analysed the dataset from Refining Ovarian Cancer Test Accuracy Scores (ROCkeTS), a single-arm prospective diagnostic test accuracy study recruiting from 24 hospitals in the UK. The aim of ROCkeTS is to validate risk prediction models in symptomatic women. We undertook an opportunistic analysis for women recruited between June 2015 to July 2022 and who were diagnosed with high grade serous ovarian cancer via the fast-track pathway. Women presenting with symptoms suspicious for ovarian cancer receive a CA125 blood test and an ultrasound scan if the CA125 level is abnormal. If either of these is abnormal, women are referred to secondary care and are seen by a gynaecologist within two weeks. Histology details were available on all women who underwent surgery or biopsy within 3 months of recruitment. Women who did not undergo surgery or biopsy at three months were followed up for 12 months as per the national guidelines in the United Kingdom. In this descriptive study, we report on patient demographics (age and menopausal status), WHO performance status, FIGO stage at diagnosis, disease distribution (low/pelvic confined, moderate/extending to mid-abdomen,

high/extending to upper abdomen) and complete cytoreduction rates in women who underwent surgery.

Results: Of 1741 participants recruited via the fast-track pathway, 119 (6.8%) were diagnosed with high grade serous ovarian cancer. The median age was 63 years (range 32 to 89). Of these, 112 (94.1%) patients had a performance status of 0 and 1, 30 (25.2%) were diagnosed with stages I/II and the disease distribution was low-to-moderate in 77 (64.7%). Complete and optimal cytoreduction were achieved in 73 (61.3%), and 18 (15.1%). The extent of disease was low in 43 of 119 (36.1%), moderate in 34 of 119 (28.6%), high in 32 of 119 (26.9%) and not available in 10 of 119 (8.4%). Nearly two thirds, that is 78 of 119 (65.5%) women with high grade serous ovarian cancer underwent primary debulking surgery, 36 of 119 (30.3%) received neoadjuvant chemotherapy followed by interval debulking surgery and 5 of 119 (4.2%) women did not undergo surgery.

Conclusion: Our results demonstrate that one in four women identified with high grade serous ovarian cancer through the fast-track pathway following symptom-triggered testing was diagnosed with early-stage disease. Symptom-triggered testing may help identify women with a low disease burden, potentially contributing to high complete cytoreduction rates.

What is already known on this topic:

Major studies have not shown any survival benefit for screening in ovarian cancer. High grade serous ovarian cancer is the most lethal form of ovarian cancer and is usually diagnosed at advanced stages.

What this study adds:

Symptom-triggered testing may contribute to the detection of high grade serous ovarian cancer at an early stage in women of good performance status and when the disease burden is low, thereby contributing to high complete cytoreduction rates.

How this study might affect research, practice or policy:

Improving community awareness of symptoms of ovarian cancer and enhanced use of the symptom-triggered testing and fast-track pathway may contribute to improved oncological outcomes for women with high grade serous ovarian cancer.

Introduction

Ovarian cancer is the sixth commonest cause of cancer-related deaths in the UK. The majority (93%) of women diagnosed with early stage ovarian cancer (FIGO stage I or II) survive beyond five years compared to only 13% diagnosed in advanced stages (stage III or IV) (CRUK). Although screening was associated with a stage shift in a major UK trial (Menon et al., 2021) , results from both the UK and US trials have not shown any mortality benefit with screening (Menon et al., 2021, Pinsky et al., 2016). There is a growing body of evidence that symptoms precede a diagnosis by between 3 and 36 months (Goff et al., 2007, Goff et al., 2004, Bankhead et al., 2008, Bankhead et al., 2005, Smith et al., 2005). However, the vague symptoms associated with ovarian cancer, as well as its low incidence, compound the challenges in its early detection (Rai et al., 2015). Goff *et al* first described a symptom triad (pain, increased abdominal size and/or bloating and early satiety) associated with ovarian cancer. This was subsequently modified to develop a symptom index which was incorporated into national guidelines to raise awareness among clinicians (NICE, 2011). Symptom-triggered testing for ovarian cancer was endorsed by cancer organisations in the United States, namely the American Cancer Society, Foundation for Women's Cancer and the Society of Gynecologic Oncology in 2007 and the United Kingdom followed suit in 2011. The National Institute of Clinical Excellence (NICE) recommended that any symptomatic women should be prioritised for testing and referred to see a gynaecologist within two weeks (fast-track pathway). The diagnostic pathway involves sequential testing of CA125 followed by a transvaginal ultrasound scan if the CA125 level is raised (NICE, 2011).

Complete tumour resection after surgery is a favourable prognosticator in women with ovarian cancer (Hoskins et al., 1994). The United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) was a trial in which women were randomised to ‘no screening’ or ‘multimodal screening’ based on their CA125 results interpreted using the Risk of Ovarian Cancer Algorithm (ROCA). Although their results did not demonstrate any overall cancer-related mortality benefit in the average-risk general population, a recent exploratory analysis showed that screening is able to detect women with high grade serous ovarian cancer at stage 1 and 2 and leads to improved short-term outcomes (Menon et al., 2023). Similarly, results from the Normal Risk Ovarian Screening Study (NROSS) demonstrated a marked stage shift whereby 70% of ROCA-detected cases of ovarian cancer and borderline tumours were stage 1 and 2 (Han et al., 2024). Detection of early-stage disease potentially results in a higher proportion of women receiving treatments including surgery and adjuvant chemotherapy. The DOvE study (Gilbert et al., 2012), a large pilot prospective study of facilitated prompt assessment of symptomatic women over 50 years demonstrated that while this approach did not reduce the number of women diagnosed with high grade serous ovarian cancer at an advanced stage, a higher rate of complete cytoreduction was achieved in women with stage 3 and 4 ovarian cancer who accessed symptom-triggered testing (36%) compared to those presenting via other pathways (21%). DOvE authors concluded that symptom-triggered testing was associated with a lower tumour burden as evidenced by the lower CA125 level in study participants.

Methods

In this descriptive study, we report on a subgroup of women recruited into ROCkeTS and who were diagnosed with high grade serous ovarian cancer via the fast-track referral pathway. We did not include other subtypes of high grade ovarian tumours such as clear cell, high grade endometrioid or carcinosarcomas as the data collection was less robust for these subtypes of OC. In particular, we describe the demographics (age and menopausal status), WHO performance status, FIGO stage at diagnosis, disease distribution (low/pelvic confined, moderate/extending to mid-abdomen, high/extending to upper abdomen) and complete cytoreduction rates in these participants. The Peritoneal Cancer Index (PCI) (Jacquet et al., 1996) and Fagotti score (Fagotti et al., 2006) were not included in this study was these were not routinely employed in the UK at the time the study was conducted. This study conforms to the STROBE Statement: guidelines for reporting observational studies.

Study protocol

ROCkeTS is an observational prospective diagnostic test accuracy study to validate risk prediction models in premenopausal and postmenopausal women with suspected ovarian cancer (Sundar et al., 2016). Participants were recruited across 24 hospitals across the UK. Women were eligible if they had a raised CA125 at primary care level, any abnormal imaging results in the community, or both. These women were recruited after a referral to hospital through the fast-track pathway, routine outpatient referrals or following emergency admissions. An information leaflet was given to all potential participants and their eligibility was checked by a doctor. Written consent was provided. Participants donated a blood sample for biomarker studies and underwent an ultrasound scan scored as per

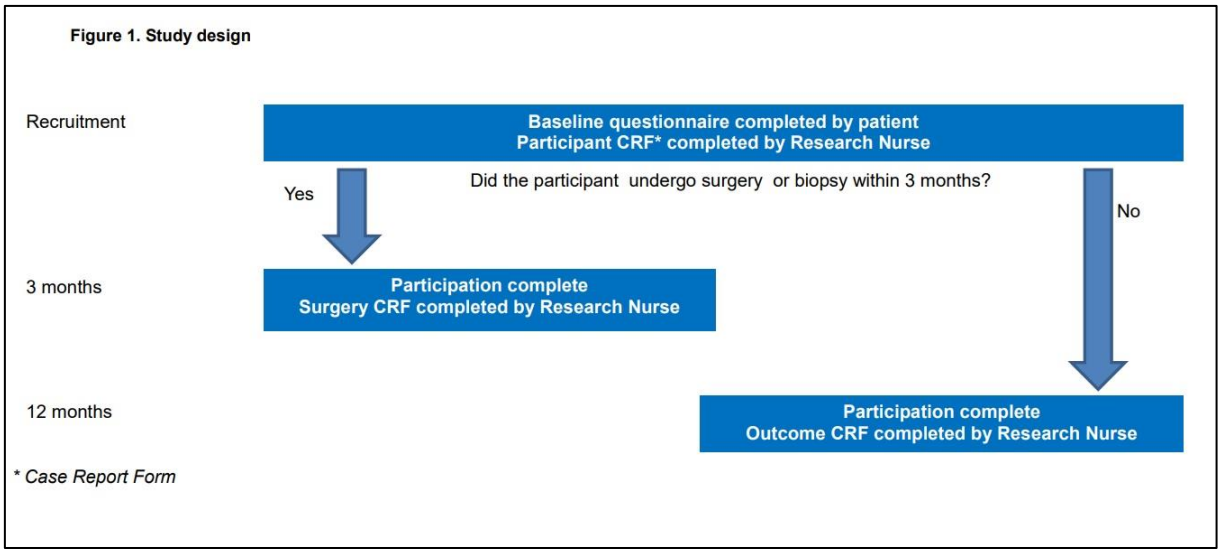
International Ovarian Tumour Analysis (IOTA) criteria by a doctor or sonographer who has completed face-to-face training in undertaking and in the interpretation of these scans.

Women completed a baseline questionnaire, and three further case report forms (participant, surgery, outcome) with details about their clinical presentation, baseline investigation results, obstetric, gynaecological, and surgical histories, and clinico-pathological outcomes such as the final histology result and treatment received were completed by the research nurse (Figure 1). The surgery case report form was completed for all women in whom a histological diagnosis was obtained at surgery or via a biopsy. The evaluation of the diagnostic accuracy of biochemical or imaging tests is underway.

Participants

Women between 16 and 90 years of age, who reported non-specific symptoms as per NICE guidelines and who had either an abnormal CA125 or ultrasound scan, or both, were recruited. Women with a current active non-ovarian malignancy, a previous history of ovarian cancer or who were pregnant were excluded. Women were followed up until either a histological diagnosis (benign, borderline, ovarian cancer, non-ovarian cancer) was attained via a biopsy or surgery at three months, and those who did not undergo biopsy or surgery were followed up at 12 months. Patients could only be recruited prior to undergoing biopsy or surgery i.e. knowledge of the biopsy result was an exclusion criteria. Women were recruited between June 2015 and March 2023 to ROCkeTS or to ROCkeTS-GEN, a sub-study whereby postmenopausal women donate a plasma sample. In our analysis, we included women recruited until July 2022. Detailed histology information and details of surgery were collected through case report forms. The study design is presented in Figure 1.

Figure 1. Study design



Data collection in the ROCkeTS study - definitions

Ovarian Cancer Staging: All cases were staged as per the FIGO Ovarian Cancer Staging System 2014.

Extent of disease: Disease spread was classified as low (pelvic and retroperitoneal spread only), moderate (extending to the abdomen but not involving the upper abdomen) and high (upper abdominal spread to upper abdominal viscera such as the diaphragm, spleen, liver, pancreas or porta hepatis).

Cytoreduction: Standard definitions were used to define the residual tumour load, namely complete resection (no visible residual disease), residual disease ≤1cm (1cm or less of disease remaining), residual disease >1cm. Unresectable cancers whereby only an exploratory laparotomy was undertaken were classed as 'inoperable'.

Fast-track pathway: This is also known as a 'two-week wait' pathway in the UK and describes an expedited pathway with timelines by which patients should be seen by

specialists and undergo further management following their referral from primary care physicians prior to the patient's appointment with a gynaecologist in hospital.

Statistical analysis

Categorical data were presented using numbers (frequencies) and proportions (percentage). The normality of distribution for continuous variables was ascertained using the Shapiro-Wilk Test and parametric variables were presented as mean and standard deviation. All analyses were performed using Stata version 17. Women with high grade serous ovarian cancer of stage 1C and above were considered as a distinct subgroup, as current national guidance advocates chemotherapy in this population (Fotopoulou, 2017).

In accordance with the journal's guidelines, we will provide our data for independent analysis by a selected team by the Editorial Team for the purposes of additional data analysis or for the reproducibility of this study in other centers if such is requested.

Results

Of the 2,596 participants in ROCkeTS, 1,741 (67.0%) were recruited via the fast-track pathway, 692 (26.7%) from outpatient clinics and 163 (6.3%) following emergency presentations. Among women presenting via the fast-track pathway, 12.3% (215/1,741) were diagnosed with primary ovarian cancer. The majority of these, that is 206 of 215 (95.8%), were epithelial tumours, 6 of 215 (2.8%) sex cord stromal tumours and 3 of 215 (1.5%) germ cell tumours. Of the 206 women with primary epithelial ovarian cancer, 87 of 215 (40.5%) were non-high grade serous ovarian cancer. These included 27 (12.6%) mucinous, 22 (10.2%) endometrioid, 17

(7.9%) clear cell, 16 (7.4%) low grade serous, 4 (1.9%) unknown and 1(0.5%) undifferentiated subtypes (Table 2).

Table 2. Stage and histological subtype distribution

FIGO stage	Number of cases	High grade serous (% by stage) n, (%)	Histological subtype	n, (%)
1	78	12 (15.4)	Epithelial	
			Mucinous	25 (32.1)
			Endometrioid	16 (20.5)
			High grade serous	12 (15.4)
			Clear cell	12 (15.4)
			Low grade serous	6 (7.7)
			Unknown	1 (1.3)
			Non-epithelial	
			Germ cell tumour	1 (1.3)
			Sex cord stromal tumour	5 (6.3)
2	25	18	Epithelial	
			High grade serous Mucinous	18 (72.0)
			Endometrioid	2 (8.0)
			Low grade serous	1 (4.0)
			Undifferentiated	2 (8.0)
				1 (4.0)
			Non-epithelial	
			Sex cord stromal tumour	1 (4.2)
3	94	75	Epithelial	
			High grade serous	75 (79.8)
			Low grade serous	7 (7.4)
			Endometrioid	5 5.3)
			Clear cell	5 (5.3)
			Unknown	1 (1.1)
			Non-epithelial	
			Germ cell tumour	1 (1.1)
4	13	11	Epithelial	
			High grade serous	11 (84.6)
			Low grade serous	1 (7.7)
			Non-epithelial	
			Germ cell tumour	1 (7.7)
NA	5	3 (100)	Epithelial	
			High grade serous	3 (60.0)
			Unknown	2 (40.0)
Total	**215**	**114 (55.1)**	**Epithelial**	
			High grade serous	**119 (55.3)**
			Mucinous	**27 (12.6)**
			Endometrioid	**22 (10.2)**
			Clear cell	**17 (7.9)**
			Low grade serous	**16 (7.4)**
			Unknown	**4 (1.8)**
			Undifferentiated	**1 (0.5)**
			Non-epithelial	
			Sex cord stromal tumour	**6 (2.8)**
			Germ cell tumour	**3 (1.5)**

A total of 119 of 1,741 (6.8%) women presenting via the fast-track pathway were diagnosed with high grade serous ovarian cancer. The median age was 63 years (range 32 to 89) and 107 of 119 (89.9%) of these women were postmenopausal. Most women, that is 112 of 119 (94.1%) were diagnosed with good performance status (0 and 1) while 6 of 119 (5.0%) had a performance status score of 2 and the performance status was unknown in 1 of 119 (0.9%). The extent of disease was low in 43 of 119 (36.1%), moderate in 34 of 119 (28.6%), high in 32 of 119 (26.9%) and not available in 10 of 119 (8.4%). Nearly two thirds, that is 78 of 119 (65.5%) women with high grade serous ovarian cancer underwent primary debulking surgery, 36 of 119 (30.3%) received neoadjuvant chemotherapy followed by interval debulking surgery and 5 of 119 (4.2%) women did not undergo surgery. Complete cytoreduction was achieved in 73 and 119 (61.3%), residual ≤1 cm in 18 of 119 (15.1%), residual >1cm in 2 of 119 (1.7%) and surgical outcomes were not available in 17 of 119 (14.3%). The disease was deemed to be inoperable in 9 of 119 (7.6%) women. Most (110 of 119 (92.4%)) participants with high grade serous ovarian cancer were stage 1C and above and 92 of 110 (83.7%) of these received chemotherapy (Table 1).

Table 1. Demographic and clinical outcomes

	N=119
Age, mean(S.D) years	65.0 (10.1)
Postmenopausal n, (%)	
Yes	107 (89.9)
No	12 (10.1)
WHO Performance Status n (%)	
0 1 2 3 4 NA	90 (75.6) 22 (18.5) 6 (5.0) 0 (0.0) 0 (0.0) 1 (0.9)
Stage n (%)	
1 2 3 4 NA	12 (10.1) 18 (15.1) 75 (63.1) 11 (9.2) 3 (2.5)
Extent n (%)	
Low Moderate High NA	43 (36.1) 34 (28.6) 32 (26.9) 10 (8.4)
Management decision n (%)	
Primary debulking surgery Interval debulking surgery No surgery	78 (65.5) 36 (30.3) 5 (4.2)
Cytoreduction rate n(%)	
Complete Residual <1cm Residual ≥1cm Inoperable NA	73 (61.3) 18 (15.1) 2 (1.7) 9 (7.6) 17 (14.3)
FIGO Stage 1C3 and above	**N=110**
Received chemotherapy n(%)	
No Yes NA	16 (14.5) 92 (83.7) 2 (1.8)

Discussion

Summary of Main Results

Women were predominantly recruited to ROCkeTS via the fast-track pathway (67.0%). Our results demonstrate that one in four women with high grade serous ovarian cancer diagnosed through the fast-track pathway were diagnosed with early-stage disease (stage I or II). The majority (94.1%) of women diagnosed with high grade serous ovarian cancer via the symptom-triggered fast-track pathway were diagnosed with a good performance status (0 and 1), with low–to-moderate disease spread (64.7%) and complete cytoreduction or residual disease ≤1cm was achieved in 76.5%. Five patients (4.2%) did not receive any treatment. Our figures demonstrate that in a real-world setting, symptom-based testing can potentially lead to diagnosis of high grade serous ovarian cancer with low disease spread and results in a high proportion of complete cytoreduction. Our results are consistent with findings from the DOvE research pilot (Gilbert et al., 2012) and demonstrate that high complete cytoreduction rates are achievable even for cases of advanced high grade serous ovarian cancer, provided that women presenting with symptoms are expedited for investigation and treatment.

Results in context of published literature

Early stage diagnosis and performance status

Some authors have questioned the benefit of symptom-based testing for ovarian cancer and hypothesised that once women experience symptoms, their disease should be presumed to be in its advanced stages and any effort to arrange earlier interventions including streamlining the route to diagnosis are therefore futile (Nagle et al., 2011). Instead, tumour biology was ascribed as the overarching

prognosticator for survival of most cases of ovarian cancer (Nagle et al., 2011, Dilley et al., 2020).Kurman *et al* suggested that ovarian cancer can be categorised as type 1 and type 2 tumours (Kurman and Shih Ie, 2010). Type 1 includes well-differentiated tumours such as mucinous, low-grade serous and endometrioid tumours. These subtypes of ovarian cancer are usually indolent and hence diagnosed in their early stages, and were initially believed to represent the majority of cases of primary ovarian cancer identified in screening trials (Kobayashi et al., 2008, Buys et al., 2011).

Our results demonstrated that 3 in 10 women diagnosed with early-stage ovarian cancer via the fast-track pathway were of the high grade serous subtype (type 2). This finding confirms that even high grade serous ovarian cancer, the most lethal subtype of ovarian cancer which usually accounts for 90% of ovarian cancer-related deaths, can be detected at an early stage in women diagnosed via the fast-track pathway following symptom-triggered testing. Results from the UKCTOCS randomised controlled trial demonstrated that multimodal screening results in a stage shift but without any survival benefit (Menon et al., 2021). Recent analysis of the trial data demonstrated for the first time that multimodal screening was able to detect a larger proportion of early stage (I and II) high grade epithelial ovarian cancer (25%) compared to the ‘no screening’ (14%) arm (Dilley et al., 2023). Our cohort and those from Dilley et al were comparable in age (median 66 years) and ethnicity (90% and above were White patients).

Our results demonstrate that similar outcomes are also attained via the symptom-based testing whereby 25.2% of cases of high grade serous ovarian cancer were diagnosed at an early stage. Firstly, these findings challenge the assumption

that the disease should always be considered to be in its advanced stages in women once they develop symptoms. More importantly, our findings emphasise the importance of increasing an awareness of ovarian cancer symptoms to facilitate earlier diagnosis via referral through the fast-track pathway to improve patient outcomes. A recent publication by Dilley *et al* (Dilley et al., 2023) demonstrated that half of women experience symptoms before the signs of ovarian cancer manifest clinically. The authors further described how women with early-stage preclinical disease most commonly experienced gastrointestinal symptoms such as a change in bowel habits and dyspepsia, as well as systemic symptoms such as fatigue. Results of the Cancer Loyalty Card Study (CLOCS) (Brewer et al., 2023), a retrospective case-control study of women with ovarian cancer demonstrated that symptoms such as indigestion or pain usually emerge up to eight months prior to the diagnosis, as evidenced by a higher purchase rate of medications for these symptoms.

Cytoreduction rates

Recent studies have demonstrated that the majority of high grade serous ovarian cancer originates from its precursor serous tubal intraepithelial carcinoma (STIC) in the fimbrial ends of the fallopian tube. This has led clinicians to question whether early detection using CA125 or pelvic ultrasound scans may actually be of value (Rai et al., 2015). In our study, nearly two thirds of women with high grade serous ovarian cancer were diagnosed when the disease distribution was low-to-moderate and complete cytoreduction was achieved in 61.3% and in 15.1% of patients, ≤1 cm residual disease was achieved at surgery. We therefore conclude that symptom-based testing may play an essential role in facilitating the early

detection of low-volume disease, and therefore high complete cytoreduction rates, as was previously proposed by the DOvE pilot study.

Strengths and Weaknesses

ROCkeTS is a prospective study and women were recruited from 24 sites across the UK. The study included over 2,500 women among whom 1,741 were recruited from the symptom- triggered fast-track pathway. ROCkeTS is the first large multicentre study that reports on the impact of symptom-triggered testing in women diagnosed with high grade serous ovarian cancer following the implementation of the fast-track pathway. Efforts were made during the data collection phase to obtain additional information for patients with missing data by contacting the patient's general practitioner or by accessing their medical records. Standard definitions were used for patient demographics, oncological outcomes and the modes of presentation to ensure that the data collection process was robust and unambiguous.

We acknowledge that our study may be subject to selection bias and that this may have resulted in the stage distribution seen in our study. We had compared the performance status, disease stage and cytoreduction rates by mode of presentation (S1) and our results did not show any significant difference among these variables by route of presentation. However, it was not possible to draw a meaningful conclusion as the number of women recruited via the emergency pathway and from other outpatient referrals were modest. Dahlberg *et al* (Dahlberg et al., 2020) demonstrated that critically unwell eligible patients are often omitted during study inclusion and identified barriers to recruitment such as practical, medical, or ethical issues from the patient or their next of kin. In our case, we presume that women with a good performance status (0 and 1) could have been preferentially approached by the research nurses. However, given that recruitment was research nurse-

led and that knowledge of histology was an exclusion criterion for the study, we believe that our findings in relation to high grade serous ovarian cancer histology cannot be exclusively attributed to selection bias.

Implications for practice and future research

Recent studies (Gajjar et al., 2012, Radu et al., 2023, Brain et al., 2014) have demonstrated a lack of understanding of the symptoms of ovarian cancer from women as well as primary care physicians across the UK. Improving community awareness of symptoms of ovarian cancer and enhanced use of the fast-track pathway are thus likely to contribute to improved oncological outcomes for women with high grade serous ovarian cancer.

Conclusion

Our results showed that one in four women with high grade serous ovarian cancer diagnosed through the fast-track pathway following symptom-triggered testing were diagnosed with early-stage disease. Symptom-triggered testing may help to identify women with low disease burden, potentially contributing to high complete cytoreduction rates and improving survival outcomes in these patients. As this is one of the largest prospective series in the UK, we consider that our data is generalizable and has implications for the UK but also other healthcare systems. These results support the current role of symptom-triggered testing to detect high grade serous ovarian cancer at good performance status and low disease load.

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Conflict of Interests: SS has received honoraria from AstraZeneca, GSK, Mercke, Immunogen and research funding from AoA diagnostics. UM had stock ownership awarded by University College London (UCL) between until October 2021 in Abcodia, which holds the licence for ROCA. She has received grants and AGM has been funded by grants from the Medical Research Council (MRC), Cancer Research UK, National Institute for Health Research (NIHR) and The Eve Appeal. UM has also received grants from UK Innovate and National Health and Medical Research Council (NHMRC), Australia and salary support from UCL Hospital Biomedical Research Centre. UM and AGM report funded research collaborations with industry - iLOF (intelligent Lab on Fiber), RNA Guardian, Micronoma, Mercy BioAnalytics and academics -Cambridge University, QIMR Berghofer Medical Research Institute Imperial College London, University of Innsbruck and Dana Farber USA. UM holds patent number EP10178345.4 for Breast Cancer Diagnostics. AGM is a member of ACED Gynaecological Cancer Working Group and is ACED Co-Director Research Domain Trials. All other authors report no conflict of interest.

Contribution to authorship:

The authors confirm contribution to the paper as follows: study conception and planning: SS, CD, CK, the ROCkeTS collaborators; data collection: the ROCkeTS collaborators; analysis and interpretation of results: FLK; SS, CD, CK draft manuscript preparation: FLK, CD, CK, SS. All authors reviewed the results and approved the final version of the manuscript.

Details of Ethics Approval:

ROCkeTS has received ethics permission from the NHS West Midlands REC (Ref14/WM/1241).

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CHAPTER 5

DISCUSSION

Research question

The challenges in the early diagnosis of OC, as a result of the non-specificity of its associated symptoms at presentation, are well recognised (Huepenbecker et al., 2021). The current testing strategy is via symptom-triggered testing (NICE, 2011). In this thesis, I undertook a scoping review which demonstrated that the psychological and clinical impacts of testing for OC are under-researched aspects of OC management. I also wished to explore the potential benefits of symptom-triggered testing via the fast-track pathway with a focus on women diagnosed with high grade serous OC, the most lethal subtype of OC (Menon et al., 2023). In particular, I wished to establish whether symptom-triggered testing was associated with the detection of high grade serous OC at an early stage when the disease is more amenable to treatment. In this thesis, I analysed the datasets from ROCkeTS and ROCkeTS-gen, a single arm prospective test accuracy study to validate risk prediction models to triage referrals for further testing in women presenting with symptoms suggestive of OC.

Summary of results

In Chapter 2, the results of a systematic literature review highlighted a number of patients, test-related and organisational factors which have been shown to be correlated with psychological morbidity during testing (screening or diagnosis) for any type of cancer. Evidence demonstrated that being non-White or non-native (Chad-Friedman et al., 2017, Bolejko et al., 2015) and having lower educational attainment (Metsälä et al., 2012, Wu et al., 2016, Yang et al., 2018, Bolejko et al., 2015, Drolet et al., 2012, Wiggins et al., 2018) were associated with higher anxiety and distress

levels across various types of cancer including breast, lung, cervical, colorectal, and OC. Past and current experiences of the testing process (Metsälä et al., 2012, Yang et al., 2018, Drolet et al., 2012, El Hachem et al., 2019, O'Connor et al., 2016) also had a psychological impact; women who had previously received abnormal results (Metsälä et al., 2012, El Hachem et al., 2019, Yang et al., 2018, Drolet et al., 2012) following screening for breast, colorectal and cervical cancers experienced higher anxiety while those who were scheduled to undergo more invasive tests (Metsälä et al., 2012, Nagendiram et al., 2020, van der Velde et al., 2017, Yang et al., 2018, O'Connor et al., 2016) (biopsies, endoscopies, colposcopies) were at greater risk of psychological distress including worry, fear and embarrassment. Finally, longer appointment waiting times (Dey et al., 2002) following an abnormal preliminary result and a lack of information (Shaikh et al., 2010) about the aim and procedural details of the testing process were associated with lower satisfaction levels and higher anxiety in women attending for breast and cervical cancer testing. From the systematic review, I identified five forms of intervention to mitigate the psychological impact of testing: the use of information aids, music therapy, real-time videos during the procedure, the presence of a patient navigator and pharmacological and homeopathic therapies. A literature review (Kwong et al., 2023) of interventions to mitigate the adverse psychological impact of testing for cancer found evidence that information aids (Hersch et al., 2015) and the presence of a patient navigator (Ferrante et al., 2008) were effective in reducing patient anxiety.

In Chapter 3, I analysed the databases from ROCkeTS and ROCkeTS-GEN (reference protocols), prospective test accuracy trials of women with non-specific symptoms, elevated CA125 and/or abnormal ultrasound. I investigated whether

variables identified from the literature review presented in Chapter 2, and other previous or current gynaecological symptoms namely a previous history of subfertility, ovarian stimulation, change in nature of periods, use of contraception, postmenopausal bleeding, current or previous use of hormone replacement therapy or number of pregnancies, could be associated with anxiety and distress in women at the time of recruitment into the study and prior to testing for OC in secondary care. Results of my analysis are compatible with a statistically significant association between younger age, higher levels of education, and presentation via the emergency routes and higher distress levels. Both women under and over 50 years reported distress levels although the former had a higher median IES-r score and this difference was statistically significant. Similarly, a higher education level was positively correlated with higher distress. This difference was statistically but not clinically significant as all participants reported severe distress. Women presenting following a routine GP referral experienced moderate distress while those who were recruited to ROCkeTS following emergency presentations experienced severe distress and this difference was statistically significant. There was no correlation between any of the considered variables and anxiety. Regarding the psychological sequelae of testing over time, results showed that women experienced moderate-to-severe anxiety and distress at recruitment and this either persisted or worsened at 12 months in 75% of women, including those who did not receive a cancer diagnosis during this time. An important finding was the significantly higher distress level associated with younger age, although women under the age of 40 years in the test accuracy trials were less likely to receive a diagnosis of OC compared to women over 40 years (1.6% versus 10.9%).

As part of dissemination, the results of Chapter 3 have already been presented at national and international cancer meetings (the European Society of Gynaecological Oncology and Cancer Research UK) to emphasise the importance of careful patient selection during testing for OC, especially in the case of premenopausal women. NICE currently advocates that women with a risk threshold of 3% should be referred via the fast-track pathway to hospital for further testing for OC (NICE, 2011). Funston (Funston et al., 2020) demonstrated that current NICE guidelines for referral for investigation of OC (NICE, 2011) based on a CA125 level of 35U/ml translates to a 1/110 (0.9%) pre-test probability of OC in women under 50 years, with only 1/308 (0.3%) of women in this age group being diagnosed with an invasive subtype of OC, including high grade serous OC. I demonstrated that the incidence of primary OC diagnosed via the fast-track pathway using a CA125 cut-off value of 35 U/ml is at least five times lower in premenopausal women (3.3% (95% CI 1.9 to 5.7)) compared to their postmenopausal counterparts (18.5% (95% CI 16.1 to 21.0)). More precisely, the incidence of OC in women under the age of 40 years was 1.6% which is below the 3% referral threshold advocated for further testing. I highlighted the importance of protecting younger women from the psychological harms of unnecessary testing for OC, as these women have a lower likelihood of OC. I further discussed the importance of communicating the difference in risk of an OC diagnosis in younger women and explore their views about a referral for further testing. Additionally, I suggested the need to review the CA125 threshold for testing and implementation of an age-stratified referral pathway. This could also improve the efficiency of the referral pathway from an NHS perspective.

In chapter 4, I demonstrated that fast track symptom-triggered testing facilitates the diagnosis of high grade serous OC at an early stage. Twenty five percent of women referred via the fast track symptom-triggered testing pathway received a diagnosis of high grade serous OC stage (1 or 2). Most (94.1%) of these women were of a good performance status (95%) and 66% presented with a 'favourable' disease distribution, namely one confined to the pelvis and abdomen where the tumour is usually more amenable to complete excision. As a result, a high rate of complete/optimal disease resection (76.4%) was achieved in these women. A high rate of complete/optimal disease resection is associated with improved survival outcomes (Hoskins et al., 1994) and this therefore translates into improved outcomes for this cohort.

Previous studies (Nagle et al., 2011) have suggested that symptom-triggered testing can only detect high grade serous OC at an advanced stage once women present with symptoms. In Chapter 4, my analysis demonstrated that 1 in 4 women referred to the fast-track pathway was diagnosed with early stage (1 & 2) OC. An earlier diagnosis in these women is associated with a favourable prognosis (Dilley et al., 2023) as these women are often clinically well, and able to tolerate the side effects of a major operation as well as additional treatment modalities such as chemotherapy during the postoperative phase. More importantly, the chances of achieving a 'successful' operation whereby all visible trace of cancer is excised (complete cytoreduction) are higher (Dilley et al., 2023).

Traditionally, the stage at diagnosis has been considered to be the overarching prognosticator for women, including those diagnosed with high grade serous OC (CRUK). Women who are diagnosed at an early stage (1 & 2) will live

longer compared to those who are diagnosed with late stage disease (3 & 4) (CRUK) as the cancer is often no longer amenable to surgical excision in the latter subgroup, or because the patient's fitness to cope with chemotherapy is significantly limited by their suboptimal performance status. Efforts have therefore been concentrated on earlier detection. In Chapter 4, I demonstrated that three quarters of participants were diagnosed with stage 3 and 4 high grade serous OC. Further analysis however demonstrated that although these women were diagnosed at later stages, they presented with a lower disease burden, were in good clinical condition (performance status 0 or 1) and complete cytoreduction rates were high. These findings support those from the DovE pilot study (Gilbert et al., 2012) where the authors did not identify a stage shift following symptom-triggered testing but instead postulated that symptom-triggered testing is conducive to the detection of high grade serous OC when the latter is less extensive and hence more surgically resectable. I therefore concluded that symptom-triggered testing may potentially contribute to the diagnosis of early stage high grade serous OC provided women recognise the 'red flag' symptoms associated with OC and present to their GPs for further testing. Satisfactory surgical outcomes may also be achievable even in women who present with late stage disease as described in Chapter 4.

Strengths and Limitations

Strengths

Chapter 2: A systematic review to evaluate the harms of cancer testing

This was the first systematic review investigating the harms of testing and effectiveness of interventions to mitigate these in patients attending for cancer

testing. All quality assessments (JBI, 2017b, JBI, 2017a, Cochrane, 2022) were undertaken in duplicate and discrepancies resolved by discussion to improve the robustness of this review. Among the criteria considered, I ensured that the inclusion criteria matched the research question for each included study, that a clear and reproducible search strategy had been adopted, that a comprehensive search was undertaken to reduce the risk of publication bias and that efforts to minimise the risk of systematic errors were described. I extended the search database to include unpublished literature. The systematic review was prospectively registered on PROSPERO.

Chapter 3 (Investigating the harms of OC testing) and 4 (Assessing the value of symptom-triggered testing in high grade serous OC)

I analysed the database from ROCkeTS and ROCkeTS-GEN for Chapters 3 and 4. Only newly presenting symptomatic women were recruited to ROCkeTS. ROCkeTS is a prospective study which adhered to a pre-specified protocol, statistical analysis plan and sample size. Women were recruited from multiple sites to minimise the risk of selection bias. ROCkeTS participants were primarily composed of patients referred from primary care to hospital for further testing. This cohort is reflective of the patient population under consideration to assess the role of symptom-triggered testing and the fast-track pathway. During the data collection phase of the study, Research Nurses were instructed to access patient medical records or to contact the GPs for women with missing data. To the best of my knowledge, Chapters 3 and 4, and ROCkeTS, are the first studies describing outcomes for women referred under the fast-track pathway.

Limitations

Chapter 2: A systematic review to evaluate the harms of cancer testing

It was not possible to undertake a meta-analysis of the results of the systematic review because of limitations in reporting of quantitative results and considerable heterogeneity in included studies with respect to cancer type, test under investigation, interventions, populations and definitions and measurement of outcomes. A further limitation of the systematic review was the underrepresentation of OC relative to other cancer types (breast, cervical, colorectal).

Chapters 3: Investigating the harms of OC testing

Selection bias

The population in ROCkeTS was ethnically homogeneous: nearly 90% of patients were White women. It is possible that native White patients could have been preferentially approached by research nurses due to logistical reasons such as language and time barriers. For instance, a consultation conducted with the assistance of an interpreter is often more time-consuming and impedes the ability of the research nurse to discuss the study due to time constraints. Alternatively, this discrepancy could be attributed to the higher anxiety and distress observed in non-native and ethnic minority women undergoing cancer testing (Nagendiram et al., 2020, Chad-Friedman et al., 2017, Bolejko et al., 2015) which led to lower participation in the test accuracy trial of these groups. My results may therefore not be representative of a subgroup of participants who could be at highest risk of anxiety and distress. Lower participation may be due to various reasons including

language, cultural and socioeconomic barriers. More importantly, it is also possible that these women were too overwhelmed at the time of their hospital appointment.

Missing patient data at 12 months

81% of screen eligible patients were recruited to ROCkeTS. In Chapter 3, only 60% of eligible patients completed the STAI-6 and IES-r questionnaires at 12 months. The low response rate at follow up could be attributed to the fact that women did not complete the final questionnaire at 12 months. One of the aims in Chapter 3 was to assess how anxiety and distress levels changed after 12 months in women who were not identified with a cancer diagnosis that is women with a false positive result at the point of referral in the community. Initially, I compared the median STAI-6 and IES-r scores at baseline and at 12 months. Feedback from the collaborators suggested that this method was problematic in view of the low response rate. I therefore presented this data using graphical representations. This strategy enabled greater clarify on (1) how scores change at recruitment and at 12 months within women who responded, and (2) illustrates the baseline scores of all women, that is women who respond at 12m and those that did not.

Lack of baseline anxiety and distress levels prior to recruitment into ROCkeTS

The pre-recruitment anxiety and distress levels of women in the community prior to their recruitment into the ROCkeTS study in hospital for OC testing were not recorded. As a result, it was not possible to ascertain whether women experienced an increase in their anxiety and distress as a result of a referral for OC testing following abnormal results, or whether these women had pre-existing high anxiety and distress levels. I therefore could not conclude whether the levels of anxiety and

distress measured were caused by testing, whether the increased distress and anxiety led to women seeking testing, or whether the levels of anxiety and distress reflect those of the female population in general. Furthermore, we did not include the onset of symptoms as part of the data collection and it is possible that the duration of symptoms may have contributed to women's anxiety and distress levels prior to their referral.

Lack of a multivariable analysis of key variables associated with psychological distress during testing

I had initially planned to undertake a multivariable analysis of the variables associated with psychological distress to assess whether there was any correlation between the different variables considered. This was not possible in view of the sample size and a univariable analysis was conducted instead.

Chapter 4: Assessing the value of symptom-triggered testing in high grade serous OC

Selection bias

A disproportionately higher number of women (68%) were recruited from the fast-track pathway with a smaller proportion recruited following referrals from other specialties (18%), General Practitioners (9%) or following emergency presentations (6%). Recruitment bias may have contributed to the stage distribution noted in my analysis. I had compared the performance status, disease stage and cytoreduction rates among women presenting via different routes but did not find any significant difference among these variables by route of presentation. It was however not possible to draw a meaningful conclusion as the number of

women recruited via other routes was considerably more modest as described earlier. Furthermore, nearly 95% of the study cohort was comprised of women with a good performance status (0 and 1). A good performance status is often associated with early stage disease, while women with more considerable symptoms and who are typically more unwell often present with more widespread disease. It is thus possible that relatively more healthy women were preferentially approached while more unwell women were excluded during the recruitment phase as a result of genuine or perceived practical, medical, or ethical obstacles as described by Dahlberg et al (Dahlberg et al., 2020).

Lack of data on patient survival

It was not possible to assess whether women who were diagnosed with high grade serous OC in the ROCkeTS study lived longer or had better survival outcomes (overall survival or progression-free survival) compared to non-participants as we did not pursue data collection beyond 12 months.

Recommendations for clinical practice

In summary, my results have highlighted findings which would contribute to a change in clinical practice and an update in the current national guidelines.

Age-stratified strategy for OC testing

The prevalence of primary OC in women under the age of 40 years is 1.6% and hence below the 3% risk threshold advocated by NICE guidelines for testing. This highlights an urgent need to review the testing pathway currently in use. Presently, all women, irrespective of age are investigated according to a universal

algorithm. I propose that the guidelines should be modified and an age-stratified diagnostic pathway extending from primary care into secondary care introduced to take into consideration this disparity in the true positive rate of OC per age group or menopausal status.

Education of public and physicians

In Chapter 4, I demonstrated that symptom-triggered testing may replicate results from screening studies whereby 25% of women with high grade serous OC could be diagnosed at early stages when treatments are more likely to be effective. This is only possible if these women recognise the symptoms associated with OC and present to their GPs and are referred for further testing promptly and appropriately. OC is a rare condition and on average, most GPs will encounter a new diagnosis of OC once every five years ((UK), 2011). One in four women will present to their GPs at least three times before they are referred to hospital for further investigations (Target-Ovarian-Cancer, 2024). These figures highlight an urgent need to educate GPs in the recognition of symptoms which should prompt a referral to hospital for OC testing especially because symptom-triggered testing may be associated with detection of OC when the disease is less widespread and hence more treatable. Similarly, enhancing an awareness of the OC symptoms via various platforms such as the media, online, newspapers, posters at GP surgeries and in public spaces among others will incentivise women to visit their GPs for further testing.

Recommendations for research

Mitigating patient anxiety

Results from my systematic review in Chapter 2 have identified three interventions which could potentially alleviate patient anxiety during the testing process: the use of information aids, decreasing waiting times by promoting the uptake of the one-stop clinic and finally, the use of patient navigators. Further research is therefore needed to evaluate whether these interventions may have the effect of mitigating anxiety in OC settings specifically, and investigate women's understanding of the OC testing process and explore their views regarding the use of adjunct which are wanted/needed to mitigate the psychological impact of a referral to hospital for OC testing via further qualitative research which would need to account for sociodemographic mediators of anxiety as shown by the results of Chapter 2.

Cohort study using national dataset

It would be helpful to undertake a cohort study of women diagnosed with high grade serous OC after 2011, that is following the introduction of symptom-based testing in the UK (NICE, 2011) from national databases including the Clinical Practice Research Datalink (CPRD) and National Cancer Registration and Analysis Service (NCRAS) and compare patient demographics, stage at diagnosis and clinical outcomes (Public-Health-England, 2016b, Herrett et al., 2015, Funston et al., 2020). These databases are more representative of the UK population. Furthermore, they present a quality-assured source of health and epidemiological data as these are derived from multiple sources (including hospitals, GP surgeries and death certificates) with a near 100% case ascertainment. This will reduce the risk of selection bias which limits the robustness of my data in Chapter 4, whereby women

of good performance status were preferentially approached by research nurses for reasons outlined earlier. Lastly, the data from national databases includes women diagnosed via multiple routes of presentations and will allow a more meaningful comparison of the performance status, disease stage and cytoreduction rates by mode of presentation as the number of women recruited from other pathways in Chapter 4 was modest.

APPENDICES

Appendix 1: Chapter 2. Search Strategy for Medline and Embase

The search strategy used for MEDLINE (Ovid) and Embase database is provided below.

(adult).ti,ab
(screen*).ti,ab
(test*).ti,ab
(detect*).ti,ab
(investigat*).ti,ab
(diagnos*).ti,ab
(biops*).ti,ab
(mass*).ti,ab
(tumo*).ti,ab
(neoplas*).ti,ab
(malignan*).ti,ab
(cancer*).ti,ab
(carcinoma*).ti,ab"
(anxiety) .ti,ab
(anxious) .ti,ab
(quality of life) .ti,ab
(satisf*).ti,ab
(worry).ti,ab
(nervous).ti,ab
(concern*).ti,ab
(fear*).ti,ab
(apprehens*).ti,ab
(psychologic*).ti,ab
(psychosocial).ti,ab
(affect*).ti,ab
(distress*).ti,ab
(stress*).ti,ab
(emotion*).ti,ab

1 AND (2 OR 3 OR 4 OR 5 OR 6 OR 7) AND (8 OR 9 OR 10 OR 11 OR 12 OR 13) AND (14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28)

Appendix 2: Chapter 2. Study Characteristics for Question 1 *'What are the effects of individual characteristics, characteristics of the testing process, and healthcare organisational factors on the psychological associations of cancer testing'*?

Table S1.1. Study characteristics of systematic reviews assessing variables associated with psychological morbidity in individuals undergoing either screening or diagnostic testing for any cancer (Question 1)

Author, year Search dates	Number of studies Total number of participants	Aim	Cancer	Test
Cazacu, 2019 NR	7 872	To evaluate current knowledge about the psychological impact of routine screening for pancreatic cancer	Pancreatic	USS, MRI, blood test.
Chad-Friedman, 2017 1946 to 2016	22 11361	(1) To synthesise the evidence on distress associated with screening tests for various cancer types. (2) To identify measures commonly used to measure distress at the time of cancer screening.	Breast Colorectal Prostate Lung Cervical	Mammogram, outpatient endoscopy, flexible sigmoidoscopy, colonoscopy
Metsälä, 2011 2000 to 2010	15 19906	(1) To identify factors associated with BC worry in women who require further testing following mammography. (2) To explore how long BC worry persists for in these women.	Breast	Further examination of mammography screening
Montgomery, 2010 1983 to 2009	30 4746	(1) To characterise manifestations and the extent of psychological distress in women with suspected BC. (2) To identify factors influencing the magnitude of psychological distress in these women.	Breast	Notification of abnormal results following mammography
Nagendiram, 2018 1991 to 2018	13 872	(1) To complete a systematic literature review of the factors that prevent Australian women from participating in cervical screening. (2) To identify factors hindering attendance at cervical screening in Australian women.	Cervical	HPV testing

Author, year Search dates	Number of studies Total number of participants	Aim	Cancer	Test
Nelson, 2016 NR	59 33532	To review studies reporting on false positive results, overdiagnosis, anxiety, pain and radiation exposure in average risk women following mammography, MRI, or USS.	Breast	Mammography, MRI, USS
O'Connor, 2016 1986 to 2014	23 4489	(1) To identify adverse psychological outcomes of colposcopy and predictors for the latter. (2) To explore how these outcomes progress over time.	Cervical	Colposcopy
van der Velde, 2017 R	7 3036	To improve our understanding of the psychological impact of a false positive CRC screening result and suggest recommendations for primary care.	Colorectal	Colonoscopy
Wu, 2016 NR	13 9416	(1) To summarize the current state of the scientific knowledge on psychological burden associated with LCS. (2) To evaluate current knowledge of the psychological cost of LCS.	Lung	Low Dose CT scan (LDCT)
Yang, 2018 2005 to 2017	58 24490	(1) To assess the extent of anxiety prior to colonoscopy or FS. (2) To explore concerns related to colonoscopy or FS. (3) To identify predictors of this anxiety. (4) To determine which interventions are helpful in mitigating this anxiety.	Colorectal	Colonoscopy, Flexible sigmoidoscopy

†Abbreviations: BC – breast cancer; CRC – colorectal cancer; FS – flexible sigmoidoscopy; HIV – Human Immunodeficiency Virus; HPV – Human Papilloma Virus; LCS – lung cancer screening; LDCT – low dose computed tomography; MRI – Magnetic Resonance Imaging; NCSP – National Cancer Screening Programme; RCT – Randomised Controlled Trial; USS – ultrasonography

Table S1.2. Study characteristics of cross-sectional studies assessing variables associated with psychological morbidity in individuals undergoing either screening or diagnostic testing for any cancer (Question 1)

Author	Country, year	Type of study N participants	Aim	Type of cancer	Test
Al-Alawi	Oman, 2019	Cross-sectional N=300	To assess the physical and psychosocial impact associated with a referral for cancer screening and identify the associated risk factors for anxiety.	Breast	Mammography
April-Sanders	USA, 2018	Cross-sectional N=230	To examine the magnitude and risk factors for BC worry in Hispanic and migrant populations.	Breast	Mammography
Bekkers	Netherlands, 2002	Cross-sectional N=47	To reduce anxiety associated with cervical cancer screening by identifying its causes, predictors, and manifestations.	Cervix	Colposcopy
Bolejko	Sweden, 2015	Cross-sectional N=399	To evaluate the predictors and psychosocial impact of a FP result as part of BC screening.	Breast	Mammography
Drolet	Canada 2011	Cross-sectional N=942	To assess the quality of life in women following an abnormal smear result and identify predictors of negative psychosocial outcomes in this population.	Cervix	Notification of abnormal smear result
El Hachem	Lebanon 2019	Cross-sectional N=100	To evaluate the psychosocial impact of benign breast biopsies on Lebanese women after a screening mammography and the effect of these biopsies on patients' attitudes toward subsequent screening.	Breast	Mammography
French	UK 2006	Cross-sectional N=427	To assess whether anxiety levels persist in women with an inadequate smear and who subsequently have a normal result and identify predictors of raised levels of distress.	Cervix	Abnormal cervical smear result

Author	Country, year	Type of study N participants	Aim	Type of cancer	Test
Gray	UK 2006	Cross-sectional N=3671	To define the extent of anxiety and depression following a low-grade abnormal smear result, identify risk factors for higher levels of anxiety, and assess whether certain subgroups of women are particularly at risk of psychosocial morbidity.	Cervix	Notification of abnormal smear result
Hilal	Germany 2017	RCT N=225	To examine whether video colposcopy is effective at reducing anxiety during colposcopy.	Cervix	Colposcopy
Kola	Ireland 2012	Cross-sectional N=164	To identify psychosocial factors that predict distress in first time attenders at colposcopy.	Cervix	Colposcopy
Liao	Taiwan 2008	Cross-sectional N=153	(1) To explore whether uncertainty and anxiety levels vary in women with suspected BC during the diagnostic period. (2) To compare anxiety and uncertainty levels between women with benign and malignant results during the diagnostic period. (3) To identify predictors of anxiety.	Breast	Breast biopsy
Maissi	UK 2004	Cross-sectional N=1376	To assess the psychosocial impact of testing for HPV following a borderline or mildly dyskaryotic smear.	Cervix	HPV testing
Medd	Australia 2005	Cross-sectional N=31	To explore men's experience of prostate biopsy and assess whether a trial of interventions to mitigate distress is feasible.	Prostate	Prostate needle biopsy
O'Connor	Ireland 2016	Cross-sectional N=584	To assess how levels of anxiety and colposcopy associated worries vary at 4, 8 and 12 months and identify predictors for these adverse outcomes.	Cervix	Colposcopy

Author	Country, year	Type of study N participants	Aim	Type of cancer	Test
Wiggins	USA 2017	Cross-sectional N=375	To explore how demographic, clinical and socio-environmental factors influence psychological responses to a false positive result for OC in asymptomatic average risk women attending for screening.	Ovary	Transvaginal USS
Wiggins	USA 2019	Cross-sectional N=373	To explore how cancer-specific distress varies with time following a false positive OC screening result.	Ovary	Transvaginal USS

†Abbreviations: BC – breast cancer; FP – false positive; HPV – Human Papilloma Virus; OC – ovarian cancer; RCT – Randomised Controlled Trials; USS – ultrasonography

Appendix 3: Chapter 2. Study Characteristics for Question 2 *'What interventions are effective at reducing the adverse psychological associations of cancer testing?'*

Table S2. Study characteristics of RCTs investigating the effectiveness of interventions for mitigating anxiety associated with cancer testing (Question 2)

Author, Country, year Type of study	Aim	Outcomes	Type of cancer	Test	Eligibility criteria	Demographics	
Camail Cameroon, 2019 Two-arm parallel group RCT	To compare anxiety levels in women undergoing a visual inspection of cervix whilst watching the procedure and those who do not.	Primary: 1. Procedure-related anxiety	Cervix	Visual inspection of cervix	Setting: Outpatient clinic in low resource area. Inclusion: 1. Women aged 30 to 49 years. 2. Cervical cancer screening programme only. 3. Informed consent. Exclusion: 1. Women unable to comply with the study protocol.	Age, mean (SD) years Education (%) Employment (%) Ethnicity Gender (%)	39.1 (5.2) I: High school (63), Elementary school (18), University (12) C: Apprenticeship (56), High school (22), None (10) Similar for I and C: Employed (65), Housewife (26). Not reported Female (100)

Author, Country, year Type of study	Aim	Outcomes	Type of cancer	Test	Eligibility criteria	Demographics	
Chantawong Thailand, 2017 Two-arm parallel group RCT	To compare pain, anxiety, and satisfaction between women, who listened to music, and those who did not during loop electrosurgical excision procedure (LEEP).	Primary: 1. Procedure related pain Secondary: 1. Procedure-related anxiety 2. Procedure-related satisfaction	Cervix	Loop electrosurgical excision procedure (LEEP)	Setting: Outpatient clinic Inclusion: 1. Adult women with confirmed or suspected high-grade changes of cervix. Exclusion: 1. Allergy to lidocaine 2. Pregnant 3. Previous major surgery to cervix or uterus 4. Cardiac pacemaker or known cardiac arrhythmia 5. Neurological conditions affecting perception of pain. 6. Previous lower urinary tract cancer 7. Coagulation disorders 8. History of drug dependence 9. Lower genital tract infection 10. Suspected cancer of cervix 11. Hearing difficulty	Age, median (range) years Education Ethnicity Gender (%)	I: 46.5 (25 to 74) C: 44.0 (25 to 63) NR NR Female (100)
Chlan USA, 2000 Two-arm parallel group RCT	To assess the effectiveness of music therapy on anxiety, discomfort, satisfaction and compliance in patients having FS.	Primary: 1. Procedure-related anxiety Secondary: 1. Procedure-related discomfort 2. Patient satisfaction 3. Adherence with screening guidelines	Colon	Flexible sigmoidoscopy	Setting: Single tertiary centre Inclusion: 1. Adult male and female 2. Screening FS 3. English as primary language 4. Minimal hearing impairment 5. Mentally competent	Age, mean (SD) years Education Ethnicity (%) Gender (%)	54.6 (11.5) NR White (96.8), African American (1.6), Hispanic (1.6) Female (69), male (31)

Author, Country, year Type of study	Aim	Outcomes	Type of cancer	Test	Eligibility criteria	Demographics	
Cruickshank UK, 2005 Two-arm parallel group RCT	To compare the effect of self-administered isoflurane and desflurane on women's experience of outpatient treatment at colposcopy.	Primary: 1. Procedure related pain, anxiety, and satisfaction. Secondary: 1. Default to follow up after treatment.	Cervix	Colposcopy	Setting: Colposcopy clinic serving regional population Inclusion: Women attending for large loop excision of transformation zone (LLETZ) for cervical intraepithelial neoplasia (CIN) Exclusion: 1. No treatment required. 2. Pregnant 3. Currently taking a monoamine–oxidase inhibitor 4. Had to drive home from the clinic themselves.	Age, mean (SD) years Education Ethnicity Gender (%)	I: 32.71 (9.78) C: 31.53 (9.12) NR NR Female (100)
de Bie Netherlands, 2011 Two-arm parallel group RCT	To assess whether provision of targeted information (by mail or phone) mitigates anxiety in women attending for colposcopy.	Primary outcome: 1. Procedure-related anxiety	Cervix	Colposcopy	Setting: Colposcopy clinic Inclusion: Adult women with abnormal smear results. Exclusion: 1. Previous colposcopy 2. Unable to attend 15 minutes before the scheduled appointment 3. Not fluent in Dutch	Age, median (IQR) years Education (%) Ethnicity Gender (%)	34.0 (30-40) At least college (47.3) NR Female (100)
Dey UK, 2002 Two-arm parallel group RCT	To determine the cost to the NHS and the impact on anxiety of a one stop clinic for assessing women with suspected BC.	Primary: 1. Procedure-related anxiety 2. Mean cost per patient	Breast	Mammography, USS, aspiration cytology, same-day results and management plan.	Setting: Teaching hospital Inclusion: Women with a breast lump and aged 35 or over	Age, mean (SD) range years Gender (%)	I: 50 (10.5), range 35-86 C: 49 (10.5), 35-95 Female (100)

Author, Country, year Type of study	Aim	Outcomes	Type of cancer	Test	Eligibility criteria	Demographics	
Domar USA, 2005 Three-arm parallel group RCT	To examine the effect of a relaxation audiotape pre- and during mammography on pain and anxiety levels.	Primary: 1. Procedure-related pain and anxiety	Breast	Mammography	Setting: Outpatient screening mammography facility in tertiary care teaching hospital Inclusion: Women attending screening mammography only. Exclusion: 1. Not fluent in English 2. Women intending to listen to own audtiotape. 3. Women who had taken pain or anxiety medication prior to their procedure, or those with an existing psychiatric condition. 4. History of BC	Age, mean years Education (%) Ethnicity (%) Gender (%)	51.7 More than high school (73-92) White (78-91), Black (7-13), other (2-10) Female (100)
Ferrante USA, 2008 Two-arm parallel group RCT	To assess the effectiveness of a patient navigator on time to diagnosis, anxiety levels, and satisfaction after an abnormal mammogram.	Primary: 1. Diagnostic interval 2. Procedure-related anxiety 3. Patient satisfaction.	Breast	Mammography	Setting: Urban university hospital serving low income minority population. Inclusion: Women with suspicious mammogram results. Exclusion: 1. Women under age 21 2. Not fluent in English.	Age mean (SD) years Education (%) Employment (%) Ethnicity (%) Gender	50.1(11.6) High school and less (76.2), College or more (23.7) Unemployed (65.7), Employed (34.4) Black (59), Hispanic (27.6), other (13.3) Female (100)

Author, Country, year Type of study	Aim	Outcomes	Type of cancer	Test	Eligibility criteria	Demographics	
Hersch Australia, 2006 Two-arm parallel group RCT	To assess whether the addition of information on overdetection improved informed choice about breast screening	Primary: 1. Informed choice about breast screening Secondary: 1. Decisional conflict 2. Confidence in decision making 3. Procedure-related anxiety 4. Worry about BC 5. Anticipated regret (later regret if do not screen) 6. Anticipated regret (later regret if do screen) 7. Temporal orientation 8. In deciding whether to have screening, how important is it for patients to consider the chance of (1) avoiding death from BC; (2) overdetection; (3) false positives 9. Perceived risk of BC 10. Perceived risk BC relative to average women 11. Compared with the average screened woman, if patients are screened how likely is it that they would (1) avoid dying from BC; (2) experience overdetection	Breast	Mammography	Setting: New South Wales Inclusion: women aged 48-50 years Exclusion: 1. Mammogram in the past 2 years 2. Previous history of BC 3. increased risk of BC e.g., strong family history 4. Language barrier.	Age mean (SD) years Country of birth (%) Education (%) Ethnicity Gender (%)	49.7 (0.4) Australia or NZ (80), abroad (20) Trade certificate or diploma (41-46), degree or graduate diploma/certificate (28-29), intermediate school certificate or less (15-17), higher school certificate (10-13). NR Female (100)

Author, Country, year Type of study	Aim	Outcomes	Type of cancer	Test	Eligibility criteria	Demographics	
Hilal Germany, 2017 Two-arm parallel group RCT	To examine whether video colposcopy reduces anxiety in patients having colposcopy.	Primary: 1. Procedure-related state anxiety Secondary: 1. Procedure-related pain 2. General unpleasantness 3. Anxiety during colposcopy 4. Satisfaction with information 5. Overall satisfaction	Cervix	Colposcopy	Setting: Hospital and doctor's office Inclusion: 1. 18 to 80 years 2. Women referred due to cervical abnormalities 3. First time attenders to colposcopy Exclusion: 1. Pregnant 2. Language barrier 3. Known anxiety disorder or depression 4. Previous treatments 5. Known cancer (any). 6. Inadequate colposcopy	Age mean (SD) years Education level* Ethnicity Gender **range 1–8 (1=minimum education required by law, 8=postgraduate education)*	I: 36.1(9.5) C: 35.5 (10.8) I: 4 (3–5) C: 3 (2–6) NR 100% female
Hilal Germany, 2018 Two-arm parallel group RCT	To assess whether music reduces anxiety in patients having colposcopy.	Primary: 1. Procedure-related anxiety Secondary: 1. Reduction of heart rate 2. Procedure-related pain 3. General unpleasantness 4. Anxiety during colposcopy 5. Overall satisfaction	Cervix	Colposcopy	Setting: Hospital and doctor's office Inclusion: 1. 18 to 80 years 2. Women referred due to cervical abnormalities 3. First time attenders to colposcopy Exclusion: 1. Pregnant 2. Language barrier 3. Known anxiety disorder or depression 4. Previous treatments 5. Known cancer (any). 6. Inadequate colposcopy	Age, mean (SD) years Educational level* Ethnicity (%) Gender (%) **range 1–8 (1=minimum education required by law, 8=postgraduate education)*	I: 36.1(9.5) C: 35.5 (10.8) I: 3 (2–3) C: 3 (2–4) German (85-92), Mediterranean (5-8), Eastern EU (4-7), Asian (2) Female (100)

Author, Country, year Type of study	Aim	Outcomes	Type of cancer	Test	Eligibility criteria	Demographics	
Lang USA, 2006 Three-arm parallel group RCT	To examine whether self-hypnotic relaxation could reduce pain and anxiety levels in patients undergoing large core needle biopsy.	Primary: 1. Procedure-related pain and anxiety	Breast	Large core needle biopsy	Setting: Urban tertiary university-affiliated medical centre Inclusion: 1. Adult male and female Exclusion: 1. Unable to give informed consent or pass screening for impaired mental function or psychosis. 2. Unable to hear or understand English.	Age, median (range) years Ethnicity (%) Gender	50 (18 –82) Caucasian (>70) Female (100)
Shaik USA, 2010 Two-arm parallel group RCT	To assess whether an educational pamphlet lowers anxiety levels before colonoscopy, and if its use affects the quality of the prep or the amount of medication used during the procedure.	Primary: 1. Procedure-related anxiety Secondary: 1. Quality of bowel preparation 2. Amount of sedative medications used.	Colorectal	Colonoscopy	Setting: Local clinic affiliated to tertiary referral centre. Inclusion: Average-risk or high-risk screening colonoscopy for the first time i.e., average-risk patients who are asymptomatic and over the age of 50, and younger patients with risk factors CRC Exclusion: 1. Previous colonoscopy 2. Not fluent in English or Spanish 3. Pregnant 4. Severe cognitive impairment or learning disability 5. On anxiolytics 6. Unable to give informed consent	Age, mean years Education Ethnicity Gender (%)	58 NR NR Female (60), male (40)

†Abbreviations

BC – breast cancer; CIN – cervical intraepithelial neoplasia; CRC – colorectal cancer; FOB – faecal occult blood; FS – flexible sigmoidoscopy; LCS – lung cancer screening; LDCT – low dose computed

tomography; LEEP - Loop electrosurgical excision procedure; LLETZ – large loop excision of transformation zone; NHS – National Health Service; USS – ultrasonography

Appendix 4: Chapter 2. Variables associated with psychological morbidity from cross-sectional studies for Question 1 *'What are the effects of individual characteristics, characteristics of the testing process, and healthcare organisational factors on the psychological associations of cancer testing?'*

Table S3. Cross Sectional Study Results: Variables associated with psychological morbidity

Author, year	Measurement tool	Variables	Results	
Al-Alawi, 2019	Psychological Capital Questionnaire (PCQ)		**Mean ± SD, p-value**	
		Age		
		- Social score	40-50	1.69 ± 2.24, p=0.008
			50-60	0.94 ± 1.67
			60	0.61 ± 1.16
		- Emotional score	p=0.189	
		- Physical score	p=0.182	
		Educational level		
		- Emotional score	p=0.553	Categories include illiterate, literate, secondary school and university graduate
		- Physical score	p=0.106	
		- Social score	0=0.405	
		Employment status		
		- Emotional score	Employed	4.17 ± 4.11, p=0.043
			Unemployed	3.26 ± 3.76
		- Social score	Employed	1.67 ± 2.23, p=0.012
			Unemployed	1.13 ± 1.88
		- Physical score	p=0.637	
		Family history of cancer		
		- Emotional score	Yes	1.67 ± 2.23, p=0.047
			No	1.13 ± 1.88
		- Physical score	Yes	1.67 ± 2.23, p=0.008
			No	1.13 ± 1.88
		- Social score	Yes	1.67 ± 2.23, p=0.007
			No	1.13 ± 1.88
April-Sanders, 2018	Self-designed questionnaire		**High vs Low/Moderate Breast Cancer Worry, OR (CI)**	
		Age at interview	0.95 (0.90-1.00)	
		Perceived Absolute Risk	1.66 (1.28 – 2.14)	
		Perceived Comparative Risk (Same/More risk compared to Lower Risk)	2.73 (1.23 – 6.06)	

Author, year	Measurement tool	Variables	Results
Bekkers, 2002	Dutch version of STAI		**STAI score (SD)**
		Experienced waiting time as short vs long	45.5 (12.9) vs 57.1 (9.7), p<0.01
		Patient has a partner vs no partner	45.3 (11.2) vs 65.0 (11.), p<0.001
		Satisfied with info from GP vs not satisfied	42.7 (12.2) vs 55.2 (12.6), p<0.05
		Satisfied with info from gynaecologist etc	38.9 (12.7) vs 50.3 (7.0), p<0.05
		Colposcopy was clearly explained	38.6 (10.0) vs 53.2 (9.8), p<0.05
		Age <40	NS (figures not reported)
		Education less than college	NS
		Cervical smear mild dyskaryosis or less	NS
		Cancer among relatives	NS
		Patient has children	NS
Bolejko, 2015	Swedish Consequences of Screening in Breast Cancer (COS-BC)		**OR (95% CI), p-value**
		<u>Worry</u>	
		- Anxiety	1.20 (1.06-1.37), p=0.005
		<u>Susceptibility</u>	
		- Anxiety	1.53 (1.21-1.95), p<0.001
		- Sense of dejection	1.49 (1.20-1.84), p<0.001
		- Behavioural	1.50 (1.21-1.87), p<0.001
		<u>Lack of social support</u>	
		- Behavioural	1.15 (1.03-1.29), p=0.016
		- Sleep	1.20 (1.06-1.35), p=0.003
		<u>Dissatisfied with own knowledge about BC</u>	
		- Sense of dejection	2.08 (1.02–4.26), p=0.045
		- Existential values	3.11 (1.45–6.67), p=0.004
		<u>Dissatisfied with information at recall</u>	
		- Sense of dejection	2.28 (1.05–4.95), p=0.037
		- Anxiety	2.56 (1.17–5.61), p=0.019
		- Behavioural	2.42 (1.12–5.24), p=0.025
		- Sleep	2.38 (1.09–5.24), p=0.031
		<u>Early recall</u>	
		- Sense of dejection	10.31 (5.01–21.23), p<0.001
		- Anxiety	6.25 (3.16–12.38), p<0.001
		- Behavioural	3.21 (1.68–6.14), p<0.001
		- Sleep	5.24 (2.72–10.07), p<0.001
		<u>Country of origin (other vs Sweden)</u>	
		- Anxiety	2.40 (1.11–5.19), p=0.026
		- Behavioural	2.96 (1.36–6.45), p=0.006
		- Sleep	3.71 (1.62–8.51) p=0.002

		Level of education (lower vs higher) Age	2.89 (1.15–7.27), p=0.024 P=NS
Drolet, 2011	STAI	 <u>Univariate analysis</u> Age Education - Elementary/high school - College - University Living - Alone - With partner - With others Household income - <$20,000 - $20,000–$49,999 - $50,000–$79,999 - ≥$80,000 Number of stressful life events - 0 - 1 - ≥2 Smoking status - Current - Former - Never Stable relationship Number of lifetime partners - 1–10 - ≥11 Screening history prior to qualifying abnormal smear - No history of abnormal smear - Prior smear was abnormal - Prior smear was normal, but already had an abnormal smear in the past Severity of abnormal smear Communication of the result	**Difference in STAI score of women with an abnormal smear result compared with women with a normal smear result., p-value (95% CI)** P=NS p=0.02 5.2 (2.4-7.9) 9.9 (7.5–12.3) 9.8 (7.2–12.4) p=0.03 11.9 (8.3–15.4) 6.8 (4.8–8.8) 9.7 (6.9–12.4) p=0.004 9.5 (6.0–12.9) 11.2 (8.5–13.9) 6.8 (3.5–10.1) 3.9 (0.7–7.2) p=0.04 7.0 (4.8–9.2) 8.8 (6.5–11.1) 12.8 (8.9–16.7) p=0.004 11.8 (9.1–14.5) 9.2 (6.4–11.9) 5.9 (3.7–8.2) P=NS p= 0.04 7.6 (5.8–9.3) 11.2 (8.1–14.4) p=0.05 9.8 (7.8–11.8) 8.9 (5.9–11.9) 5.2 (2.1–8.3) P=NS p=0.02

		- In person - By telephone/letter Woman's reported understanding of the result - Not well - Well - Very well Perceived risk of cancer compared with other women - Lower - Same - Higher - Do not know <u>Multivariate analysis</u> Household income - <$20,000 - $20,000–$49,999 - $50,000–$79,999 - ≥$80,000 Smoking status - Current - Former - Never Communication of the result - In person - By telephone/letter Woman's reported understanding of the result - Not well - Well - Very well Perceived risk of cancer compared with other women - Lower - Same - Higher	9.9 (8.1–11.8) 6.2 (3.8–8.6) p=0.003 14.2 (10.5–18.0) 8.7 (6.1–11.2) 6.8 (4.8–8.8) p=0.001 6.0 (1.5–10.6) 4.6 (1.6–7.6) 11.5 (9.2–13.8) 8.5 (5.6–11.3) p=0.03 8.7 (5.3–12.2) 1.1 (8.5–13.7) 7.1 (3.9–10.2) 5.0 (1.9–8.2) p=0.03 10.8 (8.1–13.5) 9.4 (6.7–12.1) 6.4 (4.2–8.7) p=0.01 10.1 (8.2–11.9) 6.1 (3.7–8.4) p=0.002 14.5 (10.7–18.2) 8.7 (6.2–11.3) 6.8 (4.8–8.7) p=0.01 7.5 (3.3–11.7) 5.6 (2.8–8.4) 10.9 (8.7–13.0)
El Hachem, 2019	Negative PCQ; self-designed questionnaire in Arabic	Age Religion(Christian, Druze, Muslim) Result of the last mammography - Suspicious - Benign - Normal Number of biopsies	**mean (SD), p-value** p=NR p=NR p=0.02 4.79 (6.06) 12.43 (11.20) 3.38 (6.01) p=0.02

		- 1 - 2 - 3 - 4 - 5 - 8 Date of the last biopsy - 1st 50% - 2nd 50% Worry about BC - Frequently - Often - Rarely - Never Worry affects humour - Frequently - Often - Rarely - Never Worry affects daily work - Frequently <u>Multivariate association between the negative PCQ score and variables</u> - Religion - Number of biopsies - Result last mammography - Worry - Affects humour - Affects daily work - Increases medical visits - Adherence	2.69 (5.67) 5.61 (7.64) 10.63 (9.61) 18 (9.85) 5 (0) 7 (9.90) p=0.02 6.74 (1.23) 3.20 (0.80) p=0.002 10.04 (9.62) 4 (6.61) 5.13 (6.79) 1.82 (3.88) p=0.0008 11.7 (10.6) 14.67 (11.60) 9.14 (6.94) 3 (5.33) p=0.0003 13 (10.37) p=0.55 p=0.01 p=0.01 p=0.13 p=0.80 p=0.19 p=0.14 p=0.30
Gray, 2006	HADS; MHLCS; self-designed questionnaire (POSM)	HADS anxiety subscale <u>Univariate analysis</u> Age Trial centre Marital status Employment status Training/Education Physical activity Ever had children Smoking status Index smear status Previous smear history Ethnic group (White vs Non-white) <u>Multivariate analysis</u> Age group - 20-29 years	 p=0.010 p<0.001 p=0.019 p<0.001 p=0.001 p=0.001 p=0.001 p<0.001 P=NS P=NS P=NS **OR (95% CI), p-value** p=0.031 1.00

		- 30-39 years - 40-49 years - 50-59 years Physical activity - < Once/week - 1 –3 times/week - > 3 times/week Ever had children - No - Yes Smoking status - Never smoker - Ex-smoker - Current smoker	0.97 (0.78 – 1.22) 0.85 (0.66 – 1.10) 0.68 (0.48 – 0.97) P=NR 1.00 1.13 (0.91 – 1.40) 1.52 (1.26 – 1.85) p=0.025 1.00 1.26 (1.03 – 1.55) p<0.001 1.00 1.22 (0.97 – 1.54) 1.52 (1.26 – 1.84)
Hilal, 2017	STAI	Multivariate Analyses <u>Linear</u> Study group Study center Age BMI Parity Allergies Smoking Education level <u>Logistic</u> Study group Study center Age BMI Parity Allergies Smoking Education level	 P=NS p=0.028 P=NS p=0.033 P=NS P=NS p=0.025 P=NS P=NS P=NS P=NS P=NS P=NS P=NS p=0.029 P=NS
Kola, 2012	STAI; PANAS; MBSS	<u>Multiple logistic regression</u> Age Single vs married No children vs children Less than tertiary vs tertiary education All other smear grades vs high grade Waiting time Trait anxiety Fear of minor pain Monitoring style Knowledge Expectation of pain	 P=NS p<0.05 p<0.05 P=NS P=NS p<0.05 p<0.01 p<0.05 p<0.01 p<0.05 p<0.01
Liao, 2008	Modified version of the Mishel Uncertainty in Illness Scale; STAI	Predictive Factors for Uncertainty at 3 times (reference in parentheses) Simple linear regression	

		<u>Time 1: notice of biopsy</u> - Marital status (not married) - Education (junior high and under) - Age (under 50) - Religious status (nil) - Family history of benign breast tumour (no) - Regular breast self-examination (no) - Self-perceived probability of breast cancer diagnosis (<50%) <u>Time 2: before biopsy</u> - Marital status (not married) - Education (junior high and under) - Age (under 50) - Religious status (nil) - Family history of benign breast tumour (no) - Self-perceived probability of breast cancer diagnosis (<50%) <u>Time 3: after diagnosis</u> - Marital status (not married) - Education (junior high and under) - Age (under 50) - Religious status (nil) - Family history of benign breast tumour (no) - Self-perceived probability of breast cancer diagnosis (<50%) - Biopsy result (benign)	 p=0.030 P=NS P=NS p=0.004 P=NS P=NS P=NS P=NS P=NS P=NS p=0.004 p=0.043 p=0.013 P=NS P=NS P=NS P=NS P=NS P=NS p=0.000
Maissi, 2004	STAI-6; GHQ-12; self-designed questionnaire	Linear multiple regression for predictors of <u>I. Anxiety</u> - Age (younger women vs older women) - Perceived risk of cervical cancer - Not knowing meaning of smear result	 β = - 0.11, P = 0.033 β = 0.17, P < 0.001 β = 0.17, P = 0.001

		II. Distress and concern - Perceived risk of developing cervical cancer - Not knowing the meaning of the result	 Distress: β = 0.20, P < 0.001 Concern β = 0.24, P < 0.001 Distress: β= 0.15, P < 0.001 Concern: β= 0.24, P < 0.001
Medd, 2005	Self-designed questionnaire	Men's experiences during needle biopsy of the prostate Anxiety surrounding testing - Waiting for the result - Fear of the result - Not knowing what will happen during test - Not knowing what will happen after test - Feeling helpless during test - Worry about waiting for the test Procedure related - Discomfort during test - Pain during the test - Thought of the test - Fear about coping with the test - Feeling embarrassed during test - Fear of needles - Fear of infection after test - Feeling undignified during test - Fear of bleed after test - Feeling exposed during test - Worry about opening bowels during test - Worry about passing urine during test - Feeling violated during test - Worry about not being able to see what's happening during test - Worry about the sounds of the test - Fear of bleeding during test	**% ratings ≥7/10 (where 0 =no trouble at all) and 10 =worst trouble they could imagine)** 32% 32% 13% 23% 13% 3% 32% 29% 16% 6% 16% 16% 10% 13% 0% 13% 6% 6% 10% 3% 0% 0%
O'Connor, 2016	HADS-anxiety; POSM	Multivariate analysis of predictors of anxiety	**OR (95% confidence intervals), p-value**

		over 12 months post-colposcopy Nationality - Other vs Irish Private health insurance - No vs yes History of depression - Yes vs no Satisfaction with life Per unit increase Multivariate analysis of predictors of worries about future fertility over 12 months post-colposcopy Age - 30–40 years vs <30 years - >40 years <30 years Currently pregnant - No vs yes Smoking status - Past smoker vs current smoker - Never smoked vs current smoker Multivariate analysis of predictors of worries about cervical cancer over 12 months post-colposcopy Private health insurance - No vs yes Smoking status - Past smoker vs current smoker - Never smoked vs current smoker Satisfaction with life - Per unit increase Perceived severity of colposcopy exam - Per unit increase	 p=0.020 2.13 (1.13–4.01) p=0.006 1.84 (1.20–2.84) p<0.001 2.33 (1.51–3.60) p<0.001 0.67 (0.59–0.76) p=0.002 1.26 (0.81–1.96) 0.18 (0.06–0.51) p=0.003 4.17 (1.61–10.81) p=0.012 0.49 (0.28–0.86) 0.50 (0.30–0.83) p=0.002 1.80 (1.25–2.61) p=0.012 0.52 (0.33–0.80) 0.74 (0.48–1.15) p=0.006 0.88 (0.80–0.96) p<0.001 1.84 (1.45–2.33)
Wiggins, 2017	IES; PCOS	Multivariate analyses examining factors associated with IES Scores over time	**Estimated mean ratio (95% CI), p-value**

		<u>IES-intrusion</u> Age Education - Baseline - 4-month # previous TVS tests - Baseline - 4-month Hx of abnormal TVS - Baseline - 4-month Optimism - Baseline - 4-month Social support Social constraint - Baseline - 4-month OC Family Hx in FDR <u>IES-Avoidance</u> Age Education - Baseline - 4-month # previous TVS test - Baseline - 4-month Optimism - Baseline - 4-month Social support Social constraint - Baseline - 4-month OC family history in FDR - Baseline - 4-month	P=NS p=0.014 0.93 (0.88–0.99), p<0.05 0.91 (0.85–0.98), p<0.01 p=0.021 1.00 (0.97–1.04), p=NS 0.94 (0.90–0.99), p<0.05 p=0.021 0.55 (0.35–0.87), p<0.01 0.97 (0.55–1.70), P=NS p<0.001 0.92 (0.88–0.96), p<0.001 0.95 (0.90–1.00), p<0.05 P=NS p<0.001 1.06 (1.04–1.08), p<0.001 1.11 (1.08–1.14), p<0.001 P=NS P=NS p=0.007 0.96 (0.91–1.01), P=NS 0.89 (0.83–0.96), p=0.007 p=0.013 1.00 (0.97–1.04), P=NS 0.93 (0.88–0.98), p<0.01 p=0.014 0.94 (0.91–0.98), p<0.01 0.98 (0.93–1.03), P=NS P=NS p<0.001 1.06 (1.04–1.08), p<0.001 1.14 (1.11–1.16)p<0.001 p=0.012 2.15 (1.04–4.42), p<0.05 0.64 (0.23–1.73) p=NS		
Wiggins, 2019	SF-12; IES	Multivariate association between variables and OC-specific distress trajectory membership Age Years of education - Avoidance	Medium-decreasing vs no distress OLR (95% CI) P=NS P=NS	High-decreasing vs no distress OLR (95% CI) P=NS P=NS	High-decreasing vs medium-decreasing OLR (95% CI) P=NS P=NS

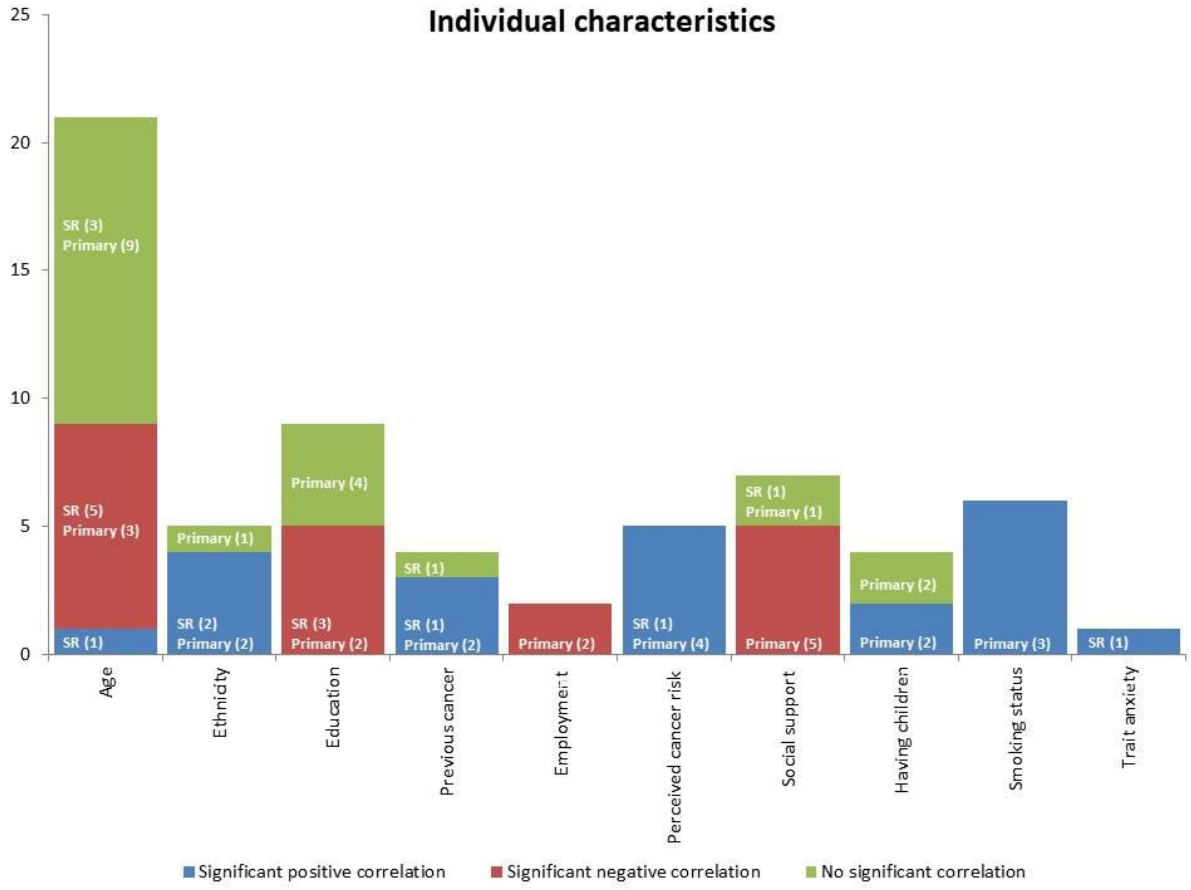
		- Intrusion	P=NS	0.85 (0.75, 0.97), p<0.05	P=NS
		# previous routine TVS			
		- Avoidance	P=NS	P=NS	P=NS
		- Intrusion	P=NS	P=NS	0.91 (0.84, 0.99), p<0.05
		No history of abnormal TVS			
		- Avoidance	2.26 (1.08, 4.75), p<0.05	P=NS	P=NS
		- Intrusion	2.60 (1.23, 5.52), p<0.05	P=NS	P=NS
		Family history of OC in FDR			
		- Avoidance	2.53 (1.34, 4.81), p<0.01	2.55 (1.10, 5.92), p<0.05	P=NS
		- Intrusion	2.91 (1.52, 5.60), p<0.05	5.41 (2.39, 12.26), p<0.01	P=NS
		Physical functioning			
		- Avoidance	P=NS	P=NS	P=NS
		- Intrusion	1.01 (1.00, 1.03), p<0.05	P=NS	P=NS
		Optimism			
		- Avoidance	P=NS	0.89 (0.80, 0.99), p<0.05	P=NS
		- Intrusion	0.91 (0.84, 0.99), p<0.05	0.77(0.69, 0.86),p<0.001	0.84 (0.77, 0.92), p<0.001
		Monitoring			
		- Avoidance	1.24 (1.05, 1.46), p<0.05	P=NS	P=NS
		- Intrusion	P=NS	1.39 (1.13, 1.70), p<0.05	P=NS
		Social support			
		- Avoidance	P=NS	P=NS	P=NS
		- Intrusion	P=NS	1.12 (1.05, 1.20), p<0.05	1.10 (1.04, 1.17), p<0.05
		Social constraint			
		- Avoidance	1.16(1.09, 1.24), p<0.001	1.29(1.21, 1.39), p<0.001	1.11 (1.07, 1.16), p<0.001
		- Intrusion	1.15 (1.09, 1.21), p<0.001	1.27(1.19, 1.36), p<0.001	1.11 (1.06, 1.16), p<0.001

†Abbreviations:

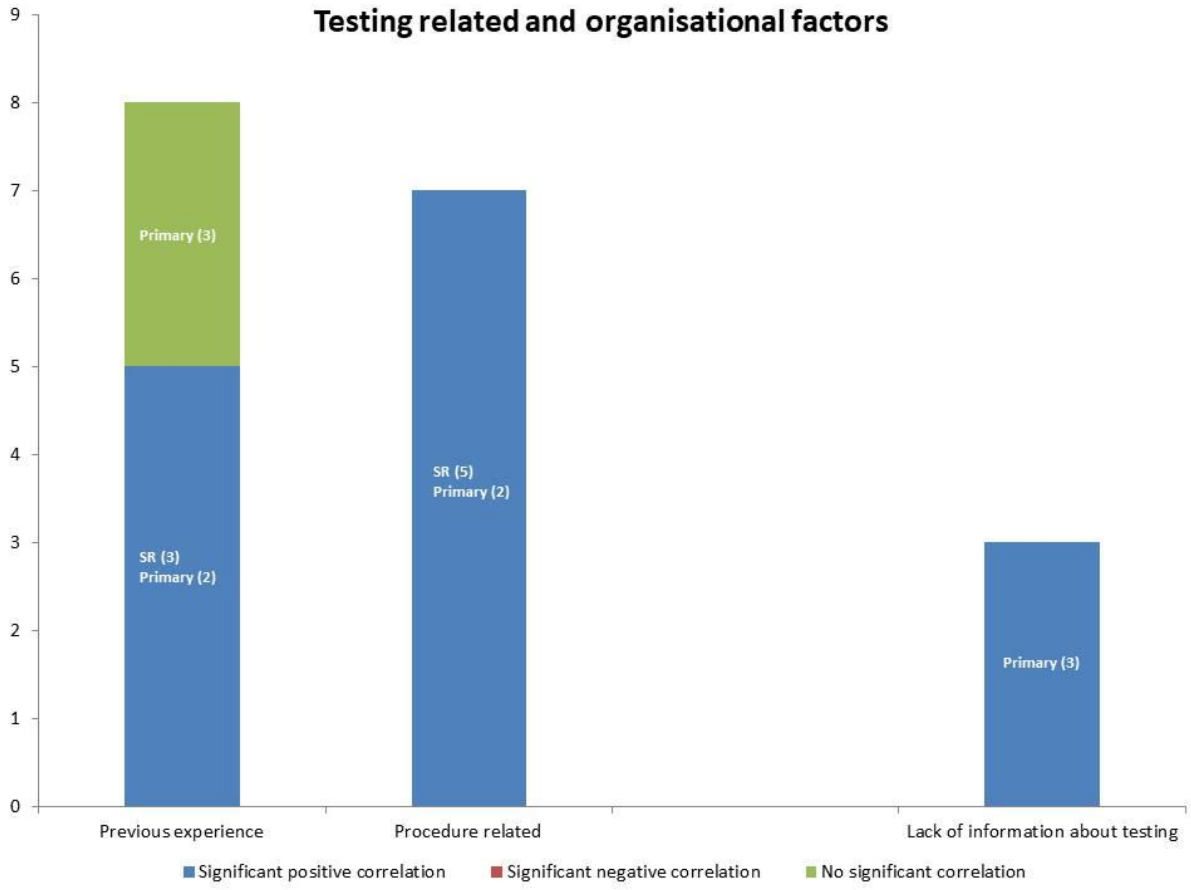
Measurement tools include COS-BC - Consequences of Screening in Breast Cancer; GHQ-12 – 12 item General Health Questionnaire; HADS – Hospital Anxiety and Depression Scale; HIP – HPV Impact Profile; IES – Impact of Event Scale; MBSS – Miller Behavioural Style Scale; MHLCS – Multi-dimensional Health Locus of Control Scale; MUIS - Mishel Uncertainty in Illness Scale; PANAS – Positive and Negative Affect Schedule; POSM - Process Outcome Specific Measure; SF – Short Form Survey; STAI - State-Trait Anxiety Inventory.

Other include OR – odds ratio; CI – confidence interval; SD – standard deviation; NS – not significant; NR – not reported; OLR – odds-like ratio; FDR – first degree relative; TVS – transvaginal ultrasonography

Appendix 5: Chapter 2. Illustration of results for Question 1*' What are the effects of individual characteristics, characteristics of the testing process, and healthcare organisational factors on the psychological associations of cancer testing?'*



Appendix 6: Chapter 2. Illustration of results for Question 1 *'What are the effects of individual characteristics, characteristics of the testing process, and healthcare organisational factors on the psychological associations of cancer testing?'*



Appendix 7: ROCkeTS Patient Information Leaflet

ROCkeTS Study

Participant Information Sheet

Clinical Study: ROCkeTS

We are inviting you to take part in the ROCkeTS study. Before you decide whether to participate it is important for you to understand what the research involves. Thank you for reading this.

What is the purpose of the study?

We know that lots of women have symptoms such as bloating and tummy discomfort. It is also very common to have cysts (balloon like swellings) on women's ovaries picked up by ultrasound. In addition, some women have higher levels of a blood test called CA125; this blood test is abnormal in lots of conditions - women with periods, fibroids, appendicitis etc. A very small number of women with ovarian cysts or abnormal CA125 will go on to be diagnosed with ovarian cancer.

The purpose of this study is to identify better tests for women with ovarian cysts or abnormal blood tests so we can pick up ovarian cancer earlier. This will also reduce unnecessary tests, hospital visits and distress in women who don't have cancer.

Why have I been invited?

We are inviting you to take part in this study because you have an ovarian cyst or a blood test indicating raised levels of CA125 in your blood. Your doctor may have referred you to

hospital because you have some common symptoms and you have had some initial tests that suggest that you need further investigation. Or you may have attended Accident and Emergency or other specialists with these symptoms. We are studying information from questionnaires, test and blood results from about 2450 patients like you, so that in the future we can be more accurate in deciding which patients with ovarian cysts and abnormal blood tests need further investigation.

Do I have to take part in this study?

It is up to you to decide whether or not you want to take part. If you decide to take part you will be asked to sign a consent form. You may choose to consent on the day that you receive this information sheet or take your time to reflect and consent at a later date. If you decide to take part you are free to withdraw at any time and without giving a reason. This will not affect any medical care you receive. If you withdraw from the study, we will retain any results from tests up to the point of withdrawal but there will be no active follow up and no testing will be carried out on any samples you have donated.

What will I need to do if I agree to take part?

If you agree to take part in this study you will be invited to complete a symptom questionnaire and donate a blood sample (up to a maximum of 20 mL, approximately the volume of a tablespoon). We will try our best to take the blood sample for research at the same time as any other usual blood tests that your doctor wants you to have. During this study you will have tests and procedures that are part of usual care. This sample will be sent to a central laboratory for testing and then be stored at the University of Birmingham biorepository. If there is time prior to your surgery you will also have a transvaginal and tummy ultrasound scan where specially trained sonographers will look for additional detail on the scan. You may need to have this scan as part of usual care anyway, in which case participating in the study just means the sonographers will record extra detail from the scan. For a few women, entering the study means having an extra scan so that the sonographers can collect the additional details needed for the study.

Follow-up: As you are scheduled for surgery or a biopsy as part of your usual care, we will collect details from the tissue analysis (histology details) for the research.

How will taking part in the study change my treatment?

Your care pathway will not be affected by taking part in this trial. Depending on previous tests you may have an additional scan, the results of which will be available to your clinical team. Your doctor will manage your care according to their clinical assessment and the standard of care guidelines.

What the possible advantages of taking part?

Your doctors will have access to the all the ultrasound scan information we are collecting and any blood tests they may have requested as part of standard care. Participating in the study may help doctors decide the best tests and treatments for other women in the future who have similar symptoms.

At this point in time, we don't know how accurate the new research tests are, so we are going to check how accurate these tests are on the blood sample we have collected from you. Therefore, the doctors treating you will not know blood test results from the research study.

What are the possible disadvantages of taking part?

The side-effects from donating a blood sample, about the volume of a tablespoonful of blood, are usually minimal – occasionally some patients may experience some bruising which settles within a day or so. Some patients can find the internal transvaginal scan a little uncomfortable – again this should settle within a short while.

Sample and image storage and future research

We will store a portion of your blood during the course of the study, as well as copies of your ultrasound images. The samples will be stored at the University of Birmingham and used for future ethically approved research studies indefinitely. The focus of these studies will be to detect and treat cancer. Researchers will have to gain permission from the study team at the University of Birmingham before being provided with any samples. As the samples will not have your name or identification it will not be possible to trace them back to you or inform you of the results. The samples may be used for genetic tests also. It is possible that collaborative researchers may include researchers working for commercial companies; researchers may be based in other countries. If you are concerned about any future research please discuss with the ROCkeTS team. It is not possible for you to take part in the study if you do not wish the samples taken to be used for future research.

The ultrasound images will be stored on secure database (MedSciNet). These images will be looked at by researchers for the purpose of quality assurance. The images may also be used for future research, focusing on detection of cancer. Researchers will have to gain permission from the study team at the University of Birmingham before being provided with any anonymised images.

National Registries

All women will also be asked in the consent form whether you agree to the researchers linking your data to the national registries about your details, beyond the 12 month participation in the trial. This will help the researchers check if the blood tests we do now can predict any medical problems in the future.

Will my GP be informed?

We will write to your GP informing him/her that you are participating in the study.

Will taking part in the study be kept confidential?

All information which is collected about you during the course of the study will be kept securely and strictly confidentially either with the University of Birmingham or on a secure system held by a third party (MedSciNet) contracted by the University of Birmingham to maintain confidentiality. Occasionally the research documentation and the results may be looked at by the people funding the research programme to check that the study is being

carried out properly. Researchers at the University of Birmingham will securely store details of your NHS number, name and address and date of birth. Your identifiable information which includes NHS number, name and address and date of birth will be used to request data to support this study from the Health and Social Care Information Centre. The data requested will be from the cancer registry, HES (hospital episodes statistics) dataset and the COSD (cancer outcomes and services dataset) to assist with our analysis.

Any information about you which is viewed by people not directly related to the research team and those parties referenced above will have your name and address removed (anonymised) so that you cannot be recognised from it. In line with clinical trial guidelines, at the end of the trial the data will be securely archived (stored) for up to 20 years.

Occasionally your study and medical records may be looked at by responsible individuals from either the University of Birmingham, hospital or from regulatory authorities where it is relevant to you taking part in this research.

Who is organising and funding the research?

The ROCkeTS study team at the University of Birmingham is organising the research in collaboration with researchers based at Universities of Keele, Bangor, University College, London and KU University, Leuven, Belgium.

For any queries about the study please contact:

ROCkeTS Trial Office, Birmingham Clinical Trials Unit (BCTU), School of Health & Population Sciences, Public Health Building, University of Birmingham, Birmingham B15 2TT Tel: 0121 415 9127
Fax: 0121 415 9135 | Email: rockets@trials.bham.ac.uk
Website: http://www.birmingham.ac.uk/ROCkeTS

The ROCkeTS study is being funded by the Department of Health through the National Institute of Health Research (NIHR). The researchers, doctors and nurses involved are not being paid for recruiting women into the study. We cannot pay women to take part either, but we will be very grateful for your participation in the study.

The University of Birmingham will be acting as the study sponsor. Representatives of the sponsor may wish to look at your medical records to ensure the proper quality assurance as part of the ROCkeTS study.

What will happen to the results of the study?

The results will be reviewed by other medical professionals and published in the medical press. The study is expected to take 4 years to complete and will start in early 2015. If we are able to identify better tests for ovarian cancer a case will be presented to the National Health Service for the tests to be used in routine care. Individuals will not be identified in any publications.

Results of the study will be posted on our website http:www.birmingham.ac.uk/ROCKETS

Also all publications from our research will be listed on this website as well as the NIHR website for this project. We will also inform the Ovarian Cancer charities, Target Ovarian Cancer, Ovacome and Ovarian Cancer Action, so that they can help disseminate the results of this research.

I want to know more about Ovarian Cancer

Both Target Ovarian Cancer - http://www.targetovariancancer.org.uk/ and Ovacome http://www.ovacome.org.uk/ are excellent sources of information on Ovarian Cancer, should you wish to know more about this disease.

Printed leaflets with further information about ovarian cancer are also available from your study consultant or your GP.

What if I want to complain about the ROCkeTS study?

Should you have a complaint about the study, contact details of an independent complaints service can be found at the front of this booklet. See 'Local PALS or equivalent local service'.

Do you have any other questions?

Having read this leaflet, we hope that you will choose to take part in the ROCkeTS Study. If you have any questions about the study now or later, feel free to ask the personnel whose names and telephone numbers are given on the front of this leaflet.

Funding acknowledgement
This project (ROCkeTS) was funded by the NIHR HTA (reference: 13/13/01)

Appendix 8: ROCkeTS Consent Form

ROCkeTS Consent Form

Trial Number: R ☐☐☐☐

Please initial each box if you agree with the statement.

Initials only please

I confirm that I have read and understand the information sheet (version _6.0__, dated__02/02/2018___). I have had an opportunity to consider the information, ask questions which have been answered satisfactorily. ☐

I understand that my participation is completely voluntary and that I am free to withdraw at any time, without giving a reason. Data collected up to the point of withdrawal will be retained within the study but I will not be contacted again by the study team. ☐

I understand that my consent form, my GP's details, my personal details (including name, address, date of birth, telephone number and NHS number) will be transferred from the Trust to the University of Birmingham. To facilitate the research this will be held securely and strictly confidentially either with the University of Birmingham or on a secure system held by a third party (MedSciNet) contracted by the University of Birmingham to maintain confidentiality. I give permission for the transfer and storage of this data ☐

I understand that the information held and maintained by University of Birmingham and other central UK NHS bodies may be used to help contact me or provide information about my health status. ☐

I agree to take part in the above study and will donate a blood sample. I understand that the blood sample will be stored at a central NHS laboratory for testing and then may be transferred for storage at the University of Birmingham biorepository. I give permission for the transfer and storage of my blood sample. ☐

I understand that my medical records and other relevant research study information may be looked at by members of the research team, representatives of the sponsor (from the University of Birmingham), the NHS trust or from regulatory authorities where it is relevant to my taking part in this research. I give permission for these individuals to have direct access to my records, including those held by my GP, if necessary. ☐

I understand that my ultrasound images and data will be sent outside the Trust and stored securely via an external database provider (https://rockets.medscinet.com/). Researchers from the University of Birmingham and the IOTA group (based in KU Leuven and King's College London) will have access to these anonymised images for the purpose of quality assurance. ☐

I understand that neither I, nor my family members will benefit financially if this research leads to the development of a new treatment or test. ☐

I consent to the researchers linking my data to national registries in the future. ☐

I agree that my blood sample be retained for ethically approved research and may be used as a reference for other clinical cases, for medical education, audit and quality control from either private or commercial companies. ☐

I understand that researchers other than those named above may carry out other ethically approved research projects (including those outside the UK), this includes genetic analysis using my anonymised samples and my anonymised data, and could also include my anonymised ultrasound images. ☐

I understand my right to confidentiality will be protected at all times. ☐

I consent to my GP being informed that I am participating in the study and being contacted if you need to trace me. ☐

Optional Consent

We would like to keep you informed about ongoing research that relies on these materials. I consent to be contacted in the future with information on research and any future research studies (optional consent). ☐

Trial Number: R ☐☐☐☐

Participant Printed Name:…… ……

Signature:……..……

Date (dd/mm/yyyy):……..

Person Informing Participant Printed name:……

Signature:……..……

Date (dd/mm/yyyy):……..

You can contact any one of the study coordinators for further information.

Original consent form to kept in site file. One copy to be sent to BCTU, one filed in the participant's clinical notes and one given to the participant to keep.

Funding acknowledgement
This project (ROCkeTS) was funded by the NIHR HTA (reference: 13/13/01)

Department of Health disclaimer
The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

D_ _D_ / M M M / _Y_ Y_Y_Y

Appendix 9: ROCkeTS Registration Form

Registration Form

This form can be completed from source data. However should any data in this form act as source data, a copy should be kept in the participant's medical notes, as well as participant's trial folder.

Part A: Participant Identifying Details

Forename, Middle initial & Surname:	Date of birth: D D / M M M / Y Y Y Y
NHS number:	Home address:
Hospital number:	
Hospital name:	Postcode:
Responsible clinician:	Phone number (inc. area code):

Part B: Clinical Information

1. Date of GP referral: D D / M M M / Y Y Y Y
2. Date of first attendance at hospital for this condition: D D / M M M / Y Y Y Y
3. Participant's height: _____cm Menopausal status: Pre-menopausal ☐
4. Participant's weight: _____Kg Post-menopausal ☐
5. Mode of Presentation: *(Choose one option only)*

Routine referral from GP	☐	-> Please complete reason for referral and U score below
2 week wait referral from GP	☐	-> Please complete reason for referral and U score below
Presentation via A&E	☐	
Referral from cancer unit as RMI>250	☐	
Referral from other speciality	☐	-> Please describe speciality:_____

If referred from GP:

What was the reason for referral?

☐ Symptoms ☐ Raised CA125 ☐ Abnormal ultrasound

☐ Palpable mass ☐ Other, please specify:_____

U score on ultrasound performed by GP:

☐ U score: _____ *(value is either 1 or 3)*

☐ Not reported or specified

Part C: Inclusion/Exclusion Criteria

Has the participant been referred to this hospital from another hospital involved in ROCkeTS?
If yes, please check that participant has not already been registered to ROCkeTS. Participant cannot be registered twice.

Inclusion criteria for both pre & postmenopausal women:

Participant is between the ages 16 and 90 years:	☐ No	☐ Yes
Participant has symptoms of Ovarian Cancer, as defined by the ROCkeTS protocol:	☐ No	☐ Yes
Does the participant have raised CA125 and/or abnormal USG? *(Please tick one option)*	☐ None	☐ Abnormal USG ☐ Raised CA125 ☐ Raised CA125 & Abnormal USG
Has the participant given written informed consent?	☐ No	☐ Yes, consent version: _____

Additional inclusion criteria for premenopausal women ONLY:

The below question should only be answered if the participant is premenopausal

Participant is scheduled to undergo surgery/biopsy for suspected ovarian cancer or adnexal mass	☐ No	☐ Yes

Exclusion criteria for both pre & postmenopausal women

Participant's USG reveals simple ovarian cysts < 5cm in size and patient does not have a raised CA125.	☐ No	☐ Yes
Participant is pregnant	☐ No	☐ Yes
Participant has had previous ovarian malignancy:	☐ No	☐ Yes
Participant has an active non-ovarian malignancy:	☐ No	☐ Yes

Additional exclusion criteria for postmenopausal women ONLY:

The below question should only be answered if the participant is postmenopausal

Participant has declined an additional transvaginal Ultrasound scan, if required:	☐ No	☐ Yes

If any shaded boxes are ticked, the participant is not eligible for registration.

Please now register the participant via telephone or online

Part D: Trial Details

Date of Registration: D D / M M M / Y Y Y Y ROCkeTS study number: R _ _ _ _

Initials of person who registered this participant: _____ Study Team Role: _____

Please continue to complete the remainder of this form

Part E: Serum Tumour Markers performed

1. By the GP BEFORE entry into ROCkeTS *Please use N/A if not applicable*	
Serum CA125:	_____ U/mL
CEA:	_____ µg/L
Ca19.9:	_____ U/mL
Ca15-3:	_____ U/mL
Beta HCG:	_____ mIU/mL
AFP:	_____ ng/mL
LDH:	_____ IU/L
He4:	_____ pmol/L
Any other markers, please specify, include units:	

2. In hospital AFTER entry into ROCkeTS *Please use N/A if not applicable*	
Serum CA 125:	_____ U/mL
CEA:	_____ µg/L
Ca19.9:	_____ U/mL
Ca15-3:	_____ U/mL
Beta HCG:	_____ mIU/mL
AFP:	_____ ng/mL
LDH:	_____ IU/L
He4:	_____ pmol/L
Any other markers, please specify, include units:	

Part F: Clinical Findings

3. Please tick either yes or no for each clinical finding

Ascites:	☐	No	☐	Yes	☐	Not Done
Pelviabdominal mass:	☐	No	☐	Yes	☐	Not Done
Breast lump:	☐	No	☐	Yes	☐	Not Done
Palpable inguinal/groin lymph nodes:	☐	No	☐	Yes	☐	Not Done
pedal oedema:	☐	No	☐	Yes	☐	Not Done

4. Is the participant a known BRCA carrier? ☐ No ☐ Yes ☐ Unknown

5. Does the participant have any of the following conditions that may account for their raised CA125 level?

Endometrosis	☐	No	☐	Yes
Diverticulitis	☐	No	☐	Yes
Polyarteritis nodosa	☐	No	☐	Yes
Pancreatitis	☐	No	☐	Yes
Rheumatoid arthritis	☐	No	☐	Yes
Osteoarthritis	☐	No	☐	Yes
Sjogrens syndrome	☐	No	☐	Yes
Hepatitis	☐	No	☐	Yes
Colitis	☐	No	☐	Yes
Other arthritis	☐	No	☐	Yes
Sarcoid	☐	No	☐	Yes
Systemic lupus erythematosus	☐	No	☐	Yes
Renal disease	☐	No	☐	Yes
Liver disease	☐	No	☐	Yes
cardiac failure	☐	No	☐	Yes
Multivisceral tuberculosis	☐	No	☐	Yes
Meigs and pseudo-Meigs syndrome	☐	No	☐	Yes

6. WHO Performance Status: _____ *(Answer should be in the range 0 to 5)*

Grade	WHO performance Status - Explanation of activity
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

7. Was the IOTA ultrasound performed as part of the GP referral ultrasound? ☐ No ☐ Yes

8. Management plan for participant *(please tick one appropriate option)*

- ☐ Keep under surveillance with follow up scans or blood tests
- ☐ Discharge from hospital
- ☐ Surgery
- ☐ Refer for cancer treatment at another hospital
- ☐ Chemotherapy alone
- ☐ Palliative
- ☐ Other specialty, please specify: _____

-> Please provide:
Name of the hospital: _____
Date of referral: D D / M M M / Y Y Y Y

Date of Management plan decision: : D D / M M M / Y Y Y Y

9. Grade of person assessing the participant *(please tick appropriate option)*

Gynaeoncologist:	☐	-> is (s)he a	☐	consultant	☐ fellow
Gynaecologist:	☐	-> is (s)he a	☐	consultant	☐ fellow
Specialist trainee or equivalent:	☐				
Clinical Nurse Specialist:	☐				

Please sign and date:

Signed: _____ Date: D D / M M M / Y Y Y Y

Appendix 10: ROCkeTS Participant Baseline Case Report Form

Participant Baseline Case Report Form

Participant Initials: __ __ __

DOB: _D _D/ _M _M _M/ _Y _Y _Y _Y

Trial Number: R ☐☐☐☐

Date form was completed: _D _D/ _M _M _M/ _Y _Y _Y _Y

Was the form completed by participant: ☐ No ☐ Yes

If no, who completed the form:_____

ROCkeTS is a national study to evaluate tests that are being carried out in association with your local hospital. You have kindly agreed to take part in the study and provide information on your symptoms and feelings. We would be grateful if you could complete the following questionnaires in this booklet. All information that you provide will be kept strictly confidential and used only for the purposes for which you have given consent.

The questionnaires are:

About yourself is series of questions about you.

Menopausal/Periods Questionnaire is a series of brief questions related to your periods to help us with understanding your menopausal status.

Surgical History is 5 short questions related gynaecological surgery history.

Obstetrics and Gynaecological History a series of short questions related to your medical history.

Six Item State-Trait Anxiety Inventory has 6 questions to measure anxiety in adults.

Impact of Events Scale – Revised has 22 questions relating to how you are feeling. Please try and complete all questions as they are presented. We want to ask you questions related to how stressful being tested and referred to hospital has been.

Symptoms Questionnaire has 17 questions relating to possible symptoms you may or may not have had. If you answer yes to any of the symptoms please try and complete the whole row. You may not remember exactly when it started; do the best you can and put approximate days when it first started within the last year. In addition we will ask 4 brief questions related to sexual symptoms.

This questionnaire should be completed at the start of the study (baseline visit) by the participant in clinic.

ROCkeTS is a Health Technology Assessment (HTA) funded Project run by the Birmingham Clinical Trials Unit (BCTU) at the University of Birmingham (www.birmingham.ac.uk/bctu).

ROCkeTS has received the West Midlands (Solihull) Multi-centre Research Ethics Committee approval and approval of the Local Research & Development Department relating to your Health Trust, Hospital and Consultant.

ABOUT YOURSELF

1. Marital status: *(Please tick one box only)*

☐ Single ☐ Living Together ☐ Married ☐ Separated/Divorced ☐ Widowed

2. Employment: *(Please tick one box only)*

☐ Employed full-time ☐ Employed part-time ☐ Self-employed

☐ Student ☐ Retired ☐ Unemployed

☐ Other, please specify: .....

3. What is the highest level of education you achieved: *(Please tick one box only)*

☐ No qualifications ☐ GCSE/ 'O' level/ NVQ1-2 ☐ 'A' level/ BTEC/ NVQ3-4

☐ University degree ☐ Postgraduate degree ☐ Other, please specify: .....

4. Ethnic group – which group best describes your ethnic group: *(Please tick one box only)*

i. Asian/Asian British:

☐ Bangladeshi ☐ Pakistani ☐ Indian

ii. Black/Black British:

☐ African ☐ Caribbean ☐ Black – other

iii. Chinese or other ethnic group:

☐ Chinese ☐ Any other ethnic group ☐ Do not wish to say

iv. White:

☐ British ☐ Irish ☐ White – other

v. Mixed:

☐ White and Asian ☐ White and Black African ☐ White and Black Caribbean

☐ Any other mixed background

5. Smoking: have you smoked more than 100 cigarettes during your lifetime? ☐ No ☐ Yes

If yes, do you currently smoke? No ☐ -> I stopped _____weeks _____months _____years ago

Yes ☐ -> I smoke about _____cigarettes a week

6. Alcohol: how many units of alcohol do you drink per week? _____ Units

Units Guide: An average pint of beer/ cider (5%) = 3 units
A 250ml glass of wine (11%) = 3 units
A single measure (25ml) of spirits (e.g. vodka or gin) = 1 unit

7. Do you have any of the following conditions/are you being treated for any of the following condition?

Endometriosis:	☐	No	☐	Yes
Adhesions:	☐	No	☐	Yes
Fibroids:	☐	No	☐	Yes
Adenomyosis:	☐	No	☐	Yes
Uterine Polyps:	☐	No	☐	Yes
High blood pressure:	☐	No	☐	Yes
Epilepsy:	☐	No	☐	Yes
Heart disease:	☐	No	☐	Yes
Arthritis:	☐	No	☐	Yes
Uterine or bladder prolapse:	☐	No	☐	Yes
Vulva pain/Vulvodynia:	☐	No	☐	Yes
Irritable bowel syndrome:	☐	No	☐	Yes
Diverticulitis:	☐	No	☐	Yes
Sexually transmitted infection:	☐	No	☐	Yes
High blood sugar – Diabetes:	☐	No	☐	Yes
Jaundice:	☐	No	☐	Yes
High blood cholesterol:	☐	No	☐	Yes
Pelvic Inflammatory disease:	☐	No	☐	Yes

Please continue to the next questionnaire on the next page.

Menopausal/Periods Questionnaire

1. Have you had periods in the last 12 months? *(Please tick the appropriate box)*

No ☐ -> Please complete Section: Post-menopausal

Yes ☐ -> Please complete Section: Pre-menopausal

Section: Pre-menopausal

If you still have periods, please answer the following questions.

2. Are you trying to get pregnant? No ☐ Yes ☐

3. Do you have any history of subfertility *(unable to conceive for more than 12 months)*? No ☐ Yes ☐

4. Do you have any history of ovarian stimulation for subfertility?
i.e. tablets (clomiphene)/IVF No ☐ Yes ☐

5. Have your periods been painful? No ☐ Yes ☐

6. Is there change in the nature or character *(i.e. more severe, lasts longer or different type) of pain with your periods?* No ☐ Yes ☐

7. Is the change in your period pain been within the last 12 months? No ☐ Yes ☐

8. Have your periods been irregular in the last 12 months? No ☐ Yes ☐

9. Have your periods been heavy in the last 12 months? No ☐ Yes ☐

10. When was your last menstrual period? D D / M M M / Y Y Y Y

11. Are you currently using contraception?

No ☐ -> Please complete Section: Surgical history

Yes ☐ -> Please select the type below:

Oral combined contraceptive pill: ☐ No ☐ Yes

Progestogen only pill *(mini pill)*: ☐ No ☐ Yes

Patch: ☐ No ☐ Yes

Vaginal ring:	☐	No	☐	Yes
Mirena Coil:	☐	No	☐	Yes
Copper IUD:	☐	No	☐	Yes
3 Monthly Progesterone injection *(depot)*:	☐	No	☐	Yes
Progesterone implant:	☐	No	☐	Yes
Barrier methods *(diaphragm, cervical cap, male condom, female condom)*:	☐	No	☐	Yes
Sterilisation *(any surgical sterilisation including a partner's vasectomy)*:	☐	No	☐	Yes
Other:	☐	No	☐	Yes, please specify below

Other, please specify:_____

Please continue to Section: Surgical history on the next page

---

Section: Post-menopausal

If your periods have stopped over 12 months ago, please complete the following questions

12. Your periods have stopped, when did they stop *(year only)*? _____

Please tick here if unknown ☐

13. Have you had any bleeding after your periods have finished? ☐ No ☐ Yes

14. Have you used Hormonal Replacement Therapy (HRT)?

No ☐

Yes ☐ -> Please specify the name: _____

When did you start using HRT (year): _____

Are you currently using HRT?

No ☐ -> When did you stop (year): _____

Yes ☐

Please continue to Section: Surgical history on the next page

Section: Surgical history

16. Have you had an operation for removal of your womb (hysterectomy)?

No ☐

Yes ☐ -> Please specify date of operation (year): .....

17. Have you had a cyst removed from your ovary by an operation (cystectomy)?

No ☐

Yes ☐ -> Please specify date of operation (year): .....

18. Have you had an operation to remove your fallopian tubes (salpingectomy)

No ☐

Yes ☐ -> Please specify date of operation (year): .....

19. Have you had an operation to remove your ovary (oophorectomy)?

No ☐

Yes ☐ -> Please specify date of operation (year): .....

How many ovaries were removed? .....

Please continue to the next questionnaire on the next page.

Other Medical History

1. Have you been diagnosed with cancer in the past?

No ☐

Yes ☐ -> Please select the type below

Breast:	☐	No	☐	Yes, date diagnosed *(year)*: _____
Colon:	☐	No	☐	Yes, date diagnosed *(year)*: _____
Ovary:	☐	No	☐	Yes, date diagnosed *(year)*: _____
Uterus:	☐	No	☐	Yes, date diagnosed *(year)*: _____
Cervix:	☐	No	☐	Yes, date diagnosed *(year)*: _____
Skin: non-melanoma:	☐	No	☐	Yes, date diagnosed *(year)*: _____
Skin: melanoma:	☐	No	☐	Yes, date diagnosed *(year)*: _____
Skin: unknown if melanoma:	☐	No	☐	Yes, date diagnosed *(year)*: _____
Lung:	☐	No	☐	Yes, date diagnosed *(year)*: _____
Stomach:	☐	No	☐	Yes, date diagnosed *(year)*: _____
Brain:	☐	No	☐	Yes, date diagnosed *(year)*: _____
Other:	☐	No	☐	Yes, please specify below

Other, please specify type and date diagnosed *(year)*: _____

_____ _____

2. Family cancer history – how many first degree relatives have had the following cancer?
(First degree relatives are parent, sibling or child)

Number of first degree relatives that have had ovarian cancer: _____

Number of first degree relatives that have had breast cancer: _____

Number of first degree relatives that have had colon cancer: _____

Number of first degree relatives that have had uterine cancer: _____

Please continue to the next questionnaire on the next page.

Obstetrics and Gynaecological History

1. Please answer the following questions *(if the answer is none, please write 0)*

How many pregnancies have you had? .....

How many live births have you had? .....

Total number of vaginal deliveries? .....

Total number of caesarean sections? .....

2. Please answer the following question *(if the answer is none, please write 0)*

How many GP visits did you attend for the current problem before being referred for testing? .....

3. Please answer the following questions on sexual activity

Are you sexually active? ☐ No ☐ Yes ☐ Do not wish to disclose

If no, is it pain and discomfort preventing you from sexual intercourse? ☐ No ☐ Yes ☐ Unknown

If yes, have you had unexplained or persistent pain during sex within the last 12 months? ☐ No ☐ Yes ☐ Unknown

How many days per month did the pain affect you? *(Please use 0 if none)* .....

How severe would you rate this pain? ☐ Mild ☐ Moderate ☐ Severe

Please continue to the next questionnaire on the next page.

Symptoms Questionnaire

Symptoms Questionnaire: Please tick yes or no. If you tick yes to any symptom please complete the whole row. Shaded boxes do not need to be rated.	No	Yes	Approximately when did these symptoms start? (mmm/yyyy)	Do you still have this? *Please tick yes or no* No	Yes	Did you tell your GP? No	Yes	If you did tell your GP, approximately when? (mmm/yyyy)	How many days in the last month have you had this? Please tick one 1 - 4 days	5 - 15 days	16 - 31 days	How severe would you rate this symptom? Please tick one Mild	Moderate	Severe
1. Have you had pelvic / abdominal pain?	N	Y	___ /____	N	Y	N	Y	___ /____						
2. Any unexpected new back pain?	N	Y	___ /____	N	Y	N	Y	___ /____						
3. Have you been vomiting (sick)?	N	Y	___ /____	N	Y	N	Y	___ /____						
4. Do you feel unusually/unexpected tired / worn out / fatigued?	N	Y	___ /____	N	Y	N	Y	___ /____						
5. Any unplanned weight loss (without diet or exercise changes)?	N	Y	___ /____	N	Y	N	Y	___ /____						
6. Is your tummy swollen?	N	Y	___ /____	N	Y	N	Y	___ /____						
7. Do clothes feel tighter around your tummy?	N	Y	___ /____	N	Y	N	Y	___ /____						
8. Are you able to feel a lump in tummy?	N	Y	___ /____	N	Y	N	Y	___ /____						
9. Do you feel a loss of appetite?	N	Y	___ /____	N	Y	N	Y	___ /____						
10. When you eat, do you feel full quickly than you used to?	N	Y	___ /____	N	Y	N	Y	___ /____						
11. Do you go to the toilet/wee more often than you used to?	N	Y	___ /____	N	Y	N	Y	___ /____						
12. When you need to wee is it a more sudden / urgent feeling than you're used to?	N	Y	___ /____	N	Y	N	Y	___ /____						
13. Have you had any constipation that is unusual to you?	N	Y	___ /____	N	Y	N	Y	___ /____						
14. Any diarrhoea / loose bowel movements that is unusual to you?	N	Y	___ /____	N	Y	N	Y	___ /____						
15. Have you had any bleeding from your bottom (rectum)?	N	Y	___ /____	N	Y	N	Y	___ /____						

Please continue to the next questionnaire on the next page.

Impact of Events Scale – Revised

Below is a list of difficulties people sometimes have after stressful life events. Please read each item, and then indicate how distressing each difficulty has been for you DURING THE PAST 7 DAYS.

The stressful event we would like you to think about is the testing you have been referred for.

0 = Not at all 1 = A little bit 2 = Moderately 3 = Quite a bit 4 = Extremely

		Please circle an answer for each question				
		Not at all	A little bit	Moderately	Quite a bit	Extremely
1	Any reminder brought back feelings about it	0	1	2	3	4
2	I had trouble staying asleep	0	1	2	3	4
3	Other things kept making me think about it	0	1	2	3	4
4	I felt irritable and angry	0	1	2	3	4
5	I avoided letting myself get upset when I thought about it or was reminded of it	0	1	2	3	4
6	I thought about it when I didn't mean to	0	1	2	3	4
7	I felt as if it hadn't happened or it wasn't real	0	1	2	3	4
8	I stayed away from reminders about it	0	1	2	3	4
9	Pictures about it popped into my mind	0	1	2	3	4
10	I was jumpy and easily startled	0	1	2	3	4
11	I tried not to think about it	0	1	2	3	4
12	I was aware that I still had a lot of feelings about it, but I didn't deal with them	0	1	2	3	4
13	My feelings about it were kind of numb	0	1	2	3	4
14	I found myself acting or feeling like I was back at that time	0	1	2	3	4
15	I had trouble falling asleep	0	1	2	3	4
16	I had waves of strong feelings about it	0	1	2	3	4
17	I tried to remove it from my memory	0	1	2	3	4
18	I had trouble concentrating	0	1	2	3	4
19	Reminders of it caused me to have physical reactions, such as sweating, trouble breathing, nausea, or a pounding heart	0	1	2	3	4
20	I had dreams about it	0	1	2	3	4
21	I felt watchful and on-guard	0	1	2	3	4
22	I tried not to talk about it	0	1	2	3	4

Please continue to the next questionnaire on the next page.

Six Items State-Trait Anxiety Inventory

A number of statements which people have used to describe themselves are given below.

Read each statement and then circle the most appropriate number to the right of the statement to indicate how you feel right now, at this moment. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

		Please circle an answer for each question			
		Not at all	Somewhat	Moderately	Very much
1	I feel calm	1	2	3	4
2	I am tense	1	2	3	4
3	I feel upset	1	2	3	4
4	I am relaxed	1	2	3	4
5	I feel content	1	2	3	4
6	I am worried	1	2	3	4

Please make sure that you have answered all of the questions.

Thank you very much for completing these questionnaires.

Appendix 11: ROCkeTS Surgery Case Report Form

Surgery Case Report Form

To be completed for participant who had surgery and/or had a biopsy

Study Number: R ☐☐☐☐ Participant initials: __ __ __ DOB: D D / M M M / Y Y Y Y

1. Did the participant have: *(Please tick all that apply)*

Biopsy: ☐ No ☐ Yes -> date of biopsy taken: D D / M M M / Y Y Y Y

Surgery: ☐ No ☐ Yes -> date of surgery: D D / M M M / Y Y Y Y

Place of surgery:
- ☐ Cancer unit
- ☐ Cancer centre
- ☐ General gynaecology service
- ☐ Other, please specify: _____

_____

2. Indication for surgery/biopsy: *(Please tick yes or no for each indication)*

Suspicion of malignancy based on ultrasound:	☐ No	☐ Yes
Suspicion of malignancy based on RMI:	☐ No	☐ Yes
Suspicion of malignancy based on other information? Please specify: _____	☐ No	☐ Yes
Surgery for likely benign pathology:	☐ No	☐ Yes

3. Were any symptoms present that were also used as an indication

Acute pain:	☐ No	☐ Yes
Chronic pain:	☐ No	☐ Yes
Suspected torsion:	☐ No	☐ Yes
Pressure symptoms:	☐ No	☐ Yes
Fertility concerns:	☐ No	☐ Yes
Participant requested operation/biopsy:	☐ No	☐ Yes

4. What was the diagnostic category:

Primary invasive malignant neoplasm *(cancer)*:	☐	-> Please complete Section: Neoplasms
Secondary malignant neoplasm *(cancer)*:	☐	-> Please complete Section: Neoplasms
Borderline neoplasm:	☐	-> Please complete Section: Neoplasms
Neoplasms of uncertain or unknown behaviour:	☐	-> Please complete Section: Neoplasms
Benign :	☐	-> Please complete Section: Benign on page 7
Normal:	☐	-> Please continue to question 22 on page 8
Other:	☐	-> Please specify: _____ then continue to question 22 on page 8
No histology:	☐	-> Please continue to question 22 on page 8

SECTION: Neoplasms

Please complete this section if you have ticked malignant, borderline or uncertain neoplasms in the question above.

5. How was the cancer diagnosed?

☐ Surgery histology ☐ Biopsy histology ☐ Cytology alone

6. Date of diagnosis of cancer *(from pathology report)*: _D _D / _M _M _M / _Y _Y _Y _Y

7. What was the management decision?

☐ Primary surgery ☐ Interval debulking

☐ No surgery ☐ other: _____

8. What was Primary cancer site?

☐ Ovarian and fallopian tube, *if yes was it:* Left ☐ Right ☐ Bilateral ☐

☐ Malignant neoplasm, primary site unknown

☐ Breast

☐ Endometrium

☐ Other genital tract

☐ Primary peritoneal

☐ Other, please specify:_____

9. Where has the diagnosis been primarily derived from?

☐ Cytology report	☐ Histology report	☐ Radiology report
☐ Hospital letter	☐ Surgery notes	☐ MDT meeting summary
☐ Death certificate	☐ Cancer registry	☐ Hospital Episode statistical data

10. Figo Stage: *(Please tick one option)*

☐ I	☐ IA	☐ IB	☐ IC	☐ IC1	☐ IC2	☐ IC3
☐ II	☐ IIA	☐ IIB	☐ III	☐ IIIA	☐ IIIA1	☐ IIIA1(i)
☐ IIIA1 (ii)	☐ IIIA2	☐ IIIB	☐ IIIC	☐ IV	☐ IVA	☐ IVB

11. Histology: Please select the option that best describe the participant's mass

Malignant Epithelial Cell Tumour	☐	-> Please complete Type: Malignant Epithelial
Germ Cell Tumour	☐	-> Please complete Type: Germ Cell Tumour
Sex Cord Stromal Tumour	☐	-> Please complete Type: Sex Cord Stromal Tumours
Metastatic Breast	☐	-> Please continue to question 12
Colon	☐	-> Please continue to question 12
Endometrium	☐	-> Please continue to question 12
Stomach	☐	-> Please continue to question 12
Cervix	☐	-> Please continue to question 12

Type: Malignant Epithelial: *(Please tick the type)*

☐ High grade serous carcinoma	☐ Mucinous carcinoma	☐ Endometroid carcinoma
☐ Low grade serous carcinoma	☐ Clear cell carcinoma	☐ Mixed mesodermal
☐ Transitional cell carcinoma	☐ Malignant brenner	☐ Small cell carcinoma
☐ Undifferentiated carcinoma		

Type: Germ Cell Tumour: *(Please tick the type)*

☐ Endodermal sinus tumour	☐ Choriocarcinoma dysgerminoma	☐ Yolk sac tumour

☐ Immature teratomas ☐ Mixed germ cell tumour ☐ Polyembryoma

Type: Sex Cord Stromal Tumours: *(Please tick the type)*

☐ Sertoli-Leydig cell tumour ☐ Granulosa cell ☐ Theca cell tumour

☐ Thecoma ☐ Fibroma ☐ Gyandroblastoma

☐ Lipid cell tumour ☐ Sex cord tumour with annular tubules

12. Extent of Disease

i. Some sites will not have access to measurements of the cancer deposit from both the CT scan and from surgery, at your site do you have access to this data from?

CT scan ☐ -> Please give the largest size of cancer deposit: _____ mm

At surgery ☐ -> Please give the largest size of cancer deposit: _____ mm

None ☐

ii. Can you describe the extent of ovarian cancer spread?
(This information can be obtained from the operating theatre notes or the preoperative imaging)

☐ Low, with pelvic and retroperitoneal spread only

☐ Moderate, additional spread to abdomen but sparing the upper abdomen

☐ High, upper abdominal disease affecting the diaphragm, spleen, liver, or pancreas or porta hepatis

iii. Is this outcome of surgery based on preoperative imaging? ☐ No ☐ Yes

iv. Is the outcome of surgery based on surgical records? ☐ No ☐ Yes

13. Outcome of surgery: What was the outcome of surgery? *(Please tick one answer only)*

Debulked to no visible residual disease ☐ -> Please continue to question 14

Debulked to ≤1cm residual disease ☐ -> Please complete Detail: Residual disease

Debulked to >1cm residual disease ☐ -> Please complete Detail: Residual disease

Inoperable *(e.g. open/close laparotomy)* ☐ -> Please continue to question 14

Detail: Residual disease

i. Max dimension of residual disease in pelvis: _____ mm

Ii. Max dimension of residual disease outside pelvis: _____ mm

14. Chemotherapy Regime

i. Did the participant have chemotherapy?	☐ No	☐ Yes
ii. Which regime was used?	☐ Carbo/Taxol	☐ Carboplatin alone
iii. Was bevazicumab also used?	☐ No	☐ Yes

15. Were any of the following performed during this surgery? *(Please tick an appropriate answer for all questions)*

i. Hysterectomy:

☐ Not performed	☐ Sub-total hysterectomy	☐ Total hysterectomy
☐ Not technically possible	☐ Previously performed	☐ Not available at site
☐ Other, please specify: _____		

ii. Salpingo-oophorectomy:

☐ Not performed	☐ Unilateral	☐ Previously performed *(Unilateral)*
☐ Not technically possible	☐ Bilateral	☐ Previously performed *(Bilateral)*
☐ Other, please specify: _____		

iii. Pelvic lymph node surgery:

☐ Not performed	☐ Sampling only	☐ Systemic lymphadenectomy

iv. Para-aortic lymph node surgery:

☐ Not performed	☐ Sampling only	☐ Systematic lymphadenectomy

v. Omentectomy:

☐ Not performed	☐ Partial/Infracolic omentectomy	☐ Complete/Supra & Infracolic omentectomy
☐ Other, please specify: _____		

vi. Stoma formation:

☐ Not performed ☐ Colostomy ☐ Ileostomy

☐ Other, please specify: _____

vii. Bowel Resection:

☐ Not performed ☐ Small Bowel resection ☐ Larger bowel resection

☐ Small and large bowel resection

viii. Urological Surgery:

☐ No ☐ Yes

16. Was a frozen section performed?

☐ No

☐ Yes -> what were the results: _____

17. Type of operation: *(Please pick one option only)*

☐ Laparotomy ☐ Operative laparoscopy ☐ Diagnostic laparoscopy

☐ Image guided biopsy

18. Surgeon Specifics: *(please pick one type and one grade)*

i. Type of Surgeon:

☐ Gynaecological oncologist ☐ Cancer unit lead ☐ General gynaecologist

☐ Colorectal Surgeon ☐ Other, please specify: _____

ii. Grade of Surgeon:

☐ Consultant ☐ Subspec fellow ☐ Registrar

☐ Other, please specify: _____

19. Was disease resected from any other anatomical areas? *(Please select an answer for each)*

i. Liver

☐ No ☐ Yes, please specify: ☐ Hepatic peritonectomy

☐ Unknown

☐ Wedge resection
☐ Partial hepatectomy
☐ Removal of isolated deposit

ii. Spleen

☐ No
☐ Unknown

☐ Yes, please specify:

☐ Splenectomy
☐ Resection of serosal disease

iii. Diaphragm

☐ No
☐ Unknown

☐ Yes, please specify:

☐ Diaphragmatic resection
☐ Removal of isolated deposit
☐ Diaphragmatic peritonectomy *(hemi-diaphragm/bilateral)*

iv. Other

☐ No

☐ Yes, please specify: _____

_____

20. Is participant in any other ovarian cancer study?

☐ No
☐ Unknown

☐ Yes, please specify: _____

_____

End of Section: Neoplasms. Please continue to question 22 on the next page.

SECTION: Benign

Please complete this section if you have ticked benign in question 4 on page 2.

21. If benign histology, please define:

☐ Serous adenofibroma
☐ Mucinous adenofibroma
☐ Endometrioid adenofibromas
☐ Brenner tumour

☐ Serous cystadenomas and fibromas
☐ Mucinous cystadenomas
☐ Mature teratoma
☐ Endometrioma

☐ Fibro thecoma ☐ Functional

☐ Other – please specify: _____

End of Section: Benign. Please continue to question 22.

22. Has participant died?

No ☐

Yes ☐ -> Please give the date of death: _D_D/_M_M_M/_Y_Y_Y_Y

Please give cause of death: 1A = _____

1B = _____

1C = _____

2 = _____

Please give autopsy finding: _____

_____

_____

_____

Please sign and insert date below:

Date form completed: _D_D/_M_M_M/_Y_Y_Y_Y Initials of person completing form: _ _ _

Signature of person completing form: _____

Thank you very much for completing this form

Appendix 12: ROCkeTS Outcome Case Report Form

Outcome Case Report Form

To be completed at 12 months after participant registration

Study Number: R ☐☐☐☐ Participant initials: _ _ _ DOB: D D / M M M / Y Y Y Y

1. Has the participant been diagnosed with ovarian cancer in the last 12 months? ☐ No ☐ Yes

If Yes, how was the cancer treated? *(please pick one option only)*

Chemotherapy only :	☐	*-> Ensure the Section: Chemotherapy only is completed*
Surgery:	☐	*-> Ensure a Surgery CRF has been completed*
Surgery Plus chemo:	☐	*-> Ensure a Surgery CRF has been completed*
Palliation:	☐	

2. Has the participant been diagnosed with non- ovarian cancer in the last 12 months?

Breast cancer:	☐ No	☐ Yes		Uterine cancer:	☐ No	☐ Yes	
Bowel – Colorectal cancer:	☐ No	☐ Yes		Lymphoma:	☐ No	☐ Yes	
Pancreatic carcinoma:	☐ No	☐ Yes		Breast cancer:	☐ No	☐ Yes	
Gastric cancer:	☐ No	☐ Yes		hepatocellular ca:	☐ No	☐ Yes	
Lung cancer:	☐ No	☐ Yes		skin cancer:	☐ No	☐ Yes	
Kidney cancer:	☐ No	☐ Yes		Other:	☐ No	☐ Yes	

If other, please specify: .....

3. Has the participant been diagnosed with any of below?

Endometriosis:	☐ No	☐ Yes		Uterine or bladder prolapse:	☐ No	☐ Yes	
Adhesions:	☐ No	☐ Yes		Vulva pain/Vulvodynia:	☐ No	☐ Yes	
Fibroids:	☐ No	☐ Yes		Irritable bowel syndrome:	☐ No	☐ Yes	
Adenomyosis:	☐ No	☐ Yes		Diverticulitis:	☐ No	☐ Yes	
Uterine Polyps:	☐ No	☐ Yes					

Please complete the next section if you have ticked chemotherapy only in question 1 above; if other option in question 1 was selected, please continue to the Section: Participant Outcome at 12 months on page 3.

Section: Chemotherapy only

Please complete if you have ticked chemotherapy only in question 1 on the previous page.

4. Date of diagnosis of cancer (from pathology report): _D _D / _M _M _M / _Y _Y _Y _Y

5. How was the cancer diagnosed? ☐ Biopsy histology ☐ Cytology alone

6. What was Primary cancer site?

☐ Ovarian and fallopian tube, is it? Left ☐ Right ☐ Bilateral ☐
☐ Malignant neoplasm, primary site unknown
☐ Breast
☐ Endometrium
☐ Other genital tract
☐ Primary peritoneal
☐ Other, please specify:.....

7. Where has the diagnosis been primarily derived from?

☐ Cytology report	☐ Histology report	☐ Radiology report
☐ Hospital letter	☐ Surgery notes	☐ MDT meeting summary
☐ Death certificate	☐ Cancer registry	☐ Hospital episode statistical data

8. Figo Stage: *(please tick one option)*

☐ I	☐ IA	☐ IB	☐ IC	☐ IC1	☐ IC2	☐ IC3
☐ II	☐ IIA	☐ IIB	☐ III	☐ IIIA	☐ IIIA1	☐ IIIA1(i)
☐ IIIA1 (ii)	☐ IIIA2	☐ IIIB	☐ IIIC	☐ IV	☐ IVA	☐ IVB

9. Chemotherapy Regime - was chemotherapy:

Given ☐ -> Please answer questions 10 - 12
Not planned ☐ -> Please continue to the next section
Planned but not given ☐ -> Please state reason: _____

_____

_____

10. Number of completed chemotherapy cycles? _____

11. Which chemotherapy regime was used? ☐ Carbo/Taxol ☐ Carboplatin alone

12. Was bevazicumab also used? ☐ No ☐ Yes

End of chemotherapy only section, please continue to the next section

---

Section: Participant outcome at 12 months

13. Please tick the appropriate option

Under Surveillance:	☐	-> Please complete Section: Under surveillance
Discharged from care:	☐	-> Please complete Section: Under surveillance & Discharged from care
Participant lost to follow up:	☐	-> Please sign and date the form on the next page
Participant withdrew Consent:	☐	-> Please sign and date the form on the next page
Other:	☐	Please specify: _____

Section: Under surveillance

Participant is under surveillance if follow up scans or blood tests having been performed since first clinic visit.

14. In the last 12 months, how many CA125 tests have been performed prior to surgery? _____

Please specify the dates and results:

E.g. 21 / Mar / 2015, 65 U/mL	__/___/____, U/mL	__/___/____, U/mL
__/___/____, U/mL	__/___/____, U/mL	__/___/____, U/mL
__/___/____, U/mL	__/___/____, U/mL	__/___/____, U/mL

15. What other investigations has the participant undergone in the last 12 months? If so, how many?

MRI:	☐	No	☐	Yes, _____
CT Scans:	☐	No	☐	Yes, _____
Additional USG scans:	☐	No	☐	Yes, _____
Blood tests:	☐	No	☐	Yes, _____
Other:	☐	No	☐	Yes, please specify type & number: _____

_____

End of Section: Under surveillance. Please sign and date the form below.

Section: Discharged from care

16. What was the reason for discharge?

☐ No change/ stable sized cyst, please give size of largest cyst_____cms and CA125 level at discharge_____U/ml

☐ Resolved with normal Ultrasound and CA125 results

☐ Other, please specify: _____

End of Section: Discharged from care. Please sign and date the form below.

Please sign and insert date:

Date form completed: D D / M M M / Y Y Y Y __ __ / __ __ __ / __ __ __ __ Initials of person completing form: __ __ __

Signature of person completing form: _____

Thank you very much for completing this form

Appendix 13: ROCkeTS 12 Months Case Report Form

Participant 12 Months Case Report Form

Participant Initials: __ __ __

DOB: __ __/__ __ __/__ __ __ __

Trial Number: R ☐☐☐☐

Date form was completed: __ __/__ __ __/__ __ __ __

Was the form completed by participant: ☐ No ☐ Yes

If no, who completed the form:_____

When you attended Hospital last year you kindly agreed to participate in the ROCkeTS study. We are now checking with you 12 months later to see what the resultant diagnosis was and the effect the testing may have had on you emotionally.

ROCkeTS is a national study to evaluate tests that are being carried out in association with your local hospital. You have kindly agreed to take part in the study and provide information on your symptoms and feelings. We would be grateful if you could complete the following questionnaires in this booklet. All information that you provide will be kept strictly confidential and used only for the purposes for which you have given consent.

The questionnaires are:

Six Item State-Trait Anxiety Inventory has 6 questions to measure anxiety in adults.

Impact of Events Scale – Revised (IES-R) has 22 questions relating to how you are feeling. Please try and complete all questions as they are presented. We want to ask you questions related to how stressful being tested and referred to hospital has been.

Medical Condition Questionnaire is a series of questions related to your medical condition specifically looking at any diagnosis of cancer and your progress within the study in the last 12 month.

This questionnaire should be completed 12 months after joining the study by the participant.

ROCkeTS is a Health Technology Assessment (HTA) funded Project and run by the Birmingham Clinical Trials Unit (BCTU) at the University of Birmingham (www.bctu.bham.ac.uk).

ROCkeTS has received the West Midlands (Solihull) Multi-centre Research Ethics Committee approval and approval of the Local Research Ethics Committee relating to your Health Trust, Hospital and Consultant.

Six Items State-Trait Anxiety Inventory

A number of statements which people have used to describe themselves are given below.

Read each statement and then circle the most appropriate number to the right of the statement to indicate how you feel right now, at this moment. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe yow present feelings best.

		Please circle an answer for each question			
		Not at all	Somewhat	Moderately	Very much
1	I feel calm	1	2	3	4
2	I am tense	1	2	3	4
3	I feel upset	1	2	3	4
4	I am relaxed	1	2	3	4
5	I feel content	1	2	3	4
6	I am worried	1	2	3	4

Please continue to the next questionnaire on the next page.

Impact of Events Scale – Revised

Below is a list of difficulties people sometimes have after stressful life events. Please read each item, and then indicate how distressing each difficulty has been for you DURING THE PAST 7 DAYS.

The stressful event we would like you to think about is the testing you have been referred for.

0 = Not at all 1 = A little bit 2 = Moderately 3 = Quite a bit 4 = Extremely

		Please circle an answer for each question				
		Not at all	A little bit	Moderately	Quite a bit	Extremely
1	Any reminder brought back feelings about it	0	1	2	3	4
2	I had trouble staying asleep	0	1	2	3	4
3	Other things kept making me think about it	0	1	2	3	4
4	I felt irritable and angry	0	1	2	3	4
5	I avoided letting myself get upset when I thought about it or was reminded of it	0	1	2	3	4
6	I thought about it when I didn't mean to	0	1	2	3	4
7	I felt as if it hadn't happened or it wasn't real	0	1	2	3	4
8	I stayed away from reminders about it	0	1	2	3	4
9	Pictures about it popped into my mind	0	1	2	3	4
10	I was jumpy and easily startled	0	1	2	3	4
11	I tried not to think about it	0	1	2	3	4
12	I was aware that I still had a lot of feelings about it, but I didn't deal with them	0	1	2	3	4
13	My feelings about it were kind of numb	0	1	2	3	4
14	I found myself acting or feeling like I was back at that time	0	1	2	3	4
15	I had trouble falling asleep	0	1	2	3	4
16	I had waves of strong feelings about it	0	1	2	3	4
17	I tried to remove it from my memory	0	1	2	3	4
18	I had trouble concentrating	0	1	2	3	4
19	Reminders of it caused me to have physical reactions, such as sweating, trouble breathing, nausea, or a pounding heart	0	1	2	3	4
20	I had dreams about it	0	1	2	3	4
21	I felt watchful and on-guard	0	1	2	3	4
22	I tried not to talk about it	0	1	2	3	4

Please continue to the next questionnaire on the next page.

Information about you medical condition

1. Have you been diagnosed with cancer in the last year? *(Please tick)*

No	☐	-> Please complete Section: No diagnosis
Yes	☐	-> Please complete Section: With diagnosis
Unknown	☐	-> Please complete Section: No diagnosis

Section: No diagnosis

If you have NOT been diagnosed with Cancer in the last 12 months, please answer the following questions.

2. Are you still under follow-up?

No	☐	-> Please provide the date you finished: D D/ M M M/ Y Y Y Y
Yes	☐	

3. Have you presented to any other hospital with the same symptoms?

No	☐	
Yes	☐	-> Name of hospital: _____

4. Have you had surgery on your ovaries in the last 12 months? ☐ No ☐ Yes

If yes, have you returned to work after surgery?
(Tick 'no' if retired or not previously in employment)

No	☐	-> Please give reason: _____
Yes	☐	-> Please provide the date you returned to work: D D/ M M M / Y Y Y Y

5. Did you undergo operation on your ovaries in a different hospital? ☐ No ☐ Yes

6. What diagnosis have the doctors given you? *(Please answer each row)*

Pelvic Inflammatory disease:	☐	No	☐	Yes	☐	Unknown
Endometriosis:	☐	No	☐	Yes	☐	Unknown
Ovarian Cyst:	☐	No	☐	Yes	☐	Unknown
Irritable bowel syndrome:	☐	No	☐	Yes	☐	Unknown
Diverticulitis:	☐	No	☐	Yes	☐	Unknown
Adenomyosis:	☐	No	☐	Yes	☐	Unknown
Fibroids:	☐	No	☐	Yes	☐	Unknown
Adhesions:	☐	No	☐	Yes	☐	Unknown
Other:	☐	No	☐	Yes, please specify below		

If other please specify:.....

7. Have you attended your GP with the same symptoms over the last 12 months

No ☐

Yes ☐ -> How many times? .....

8. Have you been referred to any other specialist in the last 12 months?

No ☐

Yes ☐ -> Which specialty:.....

End of Section: No diagnosis. Thank you very much for completing this questionnaire.

Appendix 14: ROCkeTS Results for Postmenopausal Women

A multicentre, prospective cohort study investigating the diagnostic accuracy of risk prediction models in women with symptoms of suspected ovarian cancer (The ROCkeTS Study): results for post-menopausal women

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Abstract

Background

ROCkeTS conducted a head-to-head comparison of risk prediction models Risk of Malignancy index (RMI), International Ovarian Tumor analysis models Assessment of Different NEoplasias in the ADNEXa (ADNEX), Simple Rules, SRRisk ultrasound (USS) , Risk of Malignancy algorithm (ROMA) and Ovarian Adnexal and data reporting system (ORADS) ultrasound model in symptomatic women in a 'real world' setting.

Methods

Population – newly presenting postmenopausal women with non-specific symptoms and raised CA125 and/or abnormal imaging donated blood for ROMA testing and underwent USS performed mainly by NHS sonographers who recorded IOTA model variables. Sonographers achieved certification in IOTA terminology prior to participation and underwent quality assurance.

Index tests – IOTA ADNEX model at thresholds of 3% and 10% , ROMA at multiple thresholds, RMI1 at 200, IOTA sRisk model at thresholds of 3% and 10%, IOTA simple rules, ORADS at 10%, CA125 at 35 iu/ml. Tests were conducted blinded to outcomes.

Comparator – RMI1 at 250 threshold.

Reference standard – Tissue histology/cytology within 3 months or follow-up at 12 months

Primary outcome – diagnostic accuracy in primary invasive Ovarian Cancer versus benign/normal.

Analyses - Sensitivity, specificity, c-statistic, area under Receiver operating characteristic (ROC) curve), Positive and Negative Predictive values and calibration plot.

Findings

1242 postmenopausal women were recruited from 23 hospitals of whom 215 had primary OC (17%). Compared to RMI 1 at 250, sensitivity 82.9% (95% CI: 76.7 to 88.0), specificity 87.4% (95% CI: 84.9 to 89.6), IOTA ADNEX at 10% was more sensitive (difference of 13.9, 95% CI: 7.6 to 20.2, p<0.001) but less specific (difference of 28.5, 95% CI: 24.7, 32.3, p<0.001). ROMA at 29.9% had comparable sensitivity (difference of 3.6, 95% CI: -1.9 to 9.1, p=0.2379) with lower specificity (difference of 5.2, 95% CI: 2.5 to 8.0, p=0.0001). In posthoc analysis, ORADS achieved comparable sensitivity of 76.4%% (70.1, 82.0) with significantly lower specificity of 78.3% (75.3 – 81.0).

Interpretation

Compared to RMI 250, IOTA ADNEX at 10% had higher sensitivity but significantly lower specificity whilst ROMA at manufacturer recommended threshold (29.9%) and ORADS at 10% had comparable sensitivity but reduced specificity. Gains in sensitivity are preferred over reduced specificity in postmenopausal women. IOTA ADNEX at 10% should be considered new standard of care diagnostic in OC for postmenopausal women.

Funding

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Introduction

The global incidence of ovarian cancer (OC) is estimated at around 310,000 new patients each year, with mortality at over 200,000 deaths(1). Unfortunately, the majority of patients with OC will be diagnosed at advanced stages and ten-year survival has remained static over the last decade in high income countries, at around 35% (2). Earlier, more accurate diagnosis of OC can improve survival.

OC is associated with non-specific symptoms of persistent abdominal distension/ 'bloating', feeling full and/or loss of appetite, pelvic/abdominal pain, increased urinary urgency and/or frequency, unexplained weight loss, fatigue or changes in bowel habit. Most women referred with these symptoms and abnormal tests will not have ovarian cancer; only about 3% of premenopausal women and 18% of postmenopausal women referred through rapid access referrals in the UK NHS will be diagnosed with ovarian cancer. (3) General practitioners (GP)/family physicians are encouraged to elicit a detailed history and examine such patients prior to testing women with symptoms with CA 125 tumour marker and pelvic ultrasound (USS) (4, 5). In the United Kingdom, patients with abnormal tests in the community, either CA125 or USS are referred to hospital for assessment by gynaecologists in an expedited timed pathway referred to as 'rapid access referrals'.

The majority of women with symptoms and abnormal tests will not have ovarian cancer and only about 3% of premenopausal women and 18% of postmenopausal women referred through rapid access referrals in the UK NHS will be diagnosed with ovarian cancer. (6)

Hospital gynaecologists then use risk prediction models to triage to tertiary care for specialist gynaecological cancer surgical management. Accurate triage with rapid referral at both community and hospitals is important both because women with OC managed with maximal cytoreduction surgery in specialist gynaecological cancer centres have better survival and to concentrate cancer care resource for those most at risk (7).

Multiple risk prediction models combining clinical, biomarker, and USS indicators are used in practice for triage in hospital; these include current standard of care in the UK NHS Risk of Malignancy Index 1 (RMI 1), Risk of Malignancy algorithm (ROMA), the Assessment of Different NEoplasias in the ADNEXa (ADNEX) specialist ultrasound model devised by the International Ovarian Tumour Analysis consortium (IOTA) and Ovarian Adnexal and data reporting system (ORADS) ultrasound model devised by the American Radiology association (8, 9, 10, 11).

The data underpinning these recommendations are derived from studies that predominantly include a high proportion of patients with cancer, mostly advanced stages and highly preselected patients who have been referred into cancer centres making it unclear as to whether these risk prediction models perform well in reality when used in much lower prevalence settings. ORADS was introduced into clinical practice in 2020 but has never yet been prospectively validated.

A Cochrane systematic review investigating risk prediction models for OC included 58 studies, mostly conducted in high prevalence (> 35%), specialist hospital settings with USS undertaken by experts (12). Most studies were characterised by populations with a high proportion of advanced stage cancers, where clinical suspicion of ascites and peritoneal disease is likely to trigger CT imaging and biopsy as first steps, making triage with minimally invasive prediction models irrelevant. These features limit the applicability of existing literature to non specialist hospital or community practice settings where triage tools are most utilised. Morover, a systematic review by Bossuyt et al, highlights the poor quality of diagnostic accuracy studies in OC with the majority showing 'spin' i.e the misrepresentation and overinterpretation that results in unjustified optimism in the interpretation of study results about performance of putative biomarkers. (13).

For a risk prediction model to be clinically relevant, it needs to have high diagnostic accuracy in low prevalence settings to discriminate early stage cancer from benign with accuracy ascertained in newly presenting populations. USS interpretation is influenced by practitioner expertise, thus USS models need to be evaluated when performed by non–expert practitioners who perform the majority of scans. Model performance needs to be reported separately in pre and post menopausal populations because prevalence of OC and predominant histology type differ in these groups. (6)

Refining Ovarian Cancer Test accuracy Scores investigated the accuracy of risk prediction models and scores for diagnosing OC in newly presenting, symptomatic pre and postmenopausal women with USS models performed by non-experts (14). Here, we present results for postmenopausal women.

Methods

Our report adheres to the STARD and TRIPOD checklists Appendix 1,2, (15) (16)

Participants

Newly presenting postmenopausal women referred to hospital with non specific symptoms as described by NICE guidance (5) and raised CA125/ abnormal community USS were prospectively and consecutively recruited from 23 hospitals within the UK. Patients were recruited at outpatient clinics (rapid access referrals, USS clinics, routine primary care referrals or cross specialty referrals), or as inpatients through emergency presentations to secondary care. ROCkeTS received ethical approval from NHS West Midlands REC (14/WM/1241) and is registered on the controlled trials website (ISRCTN17160843). Trial protocol was published. (14)

Exclusion criteria were patients with USS showing simple ovarian cysts <5cm in size (very low risk of malignancy), with normal CA125, pregnancy, active non ovarian malignancy or previous ovarian malignancy.

Perimenopausal were classified into dichotomous groups of pre, or postmenopausal groups based on a patient expressed history of vaginal bleeding to enable accurate analysis as most of the risk prediction models either have different thresholds by menopausal status or incorporate different covariates based on menopausal status. No screen eligible and willing patients were excluded.

Testing

All patients completed a symptom questionnaire, donated a blood sample and underwent transabdominal and transvaginal USS scan, which formed the components of the index tests.

Index tests were: ROMA combines CA125 and He4 tumour markers, 29.9% is manufacturer recommended but various thresholds are known, 14.4%, 25.3%, 27.7%. (12) Several USS models were evaluated: IOTA ADNEX (Primary threshold: 10%, secondary threshold: 3%), IOTA simple rules, IOTA sRRisk model (Primary threshold: 10%, secondary threshold: 3%) (10, 17, 18, 19, 20). CA125 at a threshold of 35 U/ml was also evaluated. Comparator test was Risk of Malignancy index 1 which combines CA125 and limited ultrasound features, threshold 250. This was selected as comparator test as RMI 1 is the current standard of care diagnostic in the UK NHS and is used in routine practice to triage patients to gynaecological cancer centres. (11) We also investigated RMI 1 as an index test at 200 threshold.

ORADS is a scoring system based on a set of expert consensus agreed variables based on data from IOTA studies and was devised in 2020 after completion of ROCkeTS recruitment. In posthoc analyses, IOTA variables from the ROCkeTS USS case report form were mapped on to the ORADS lexicon using methodology described previously to calculate ORADS scores(threshold 10% ORADS lexicon 1-3 versus 4-5). (21). Appendix page 41

Serum were collected as per predefined standard operating procedure, transported and stored at -80C until analysis at NHS South Tyne and Wear Pathology Services labs. For analysis, samples were thawed in batches. Testing for HE4 and CA125 was performed on Roche Cobas e802 modules as per manufacturer recommendations. CA125 and HE4 were measured using electrochemiluminescence immuno-assay (ECLIA) technology, according to the manufacturers' instructions. Roche Elecsys assay kits were obtained from Roche Diagnostics.

Ultrasound training and Quality assurance

Sonographers in participating sites received one day in-person and online USS training and examined. USS within ROCkeTS was permitted only by those who passed IOTA certification. Quality assessment (QA) was conducted by the IOTA team to assess whether imaging was annotated as per IOTA terminology. Scan was performed mainly by level II ultrasound examiners (non medical sonographers). However, no minimum experience was stipulated for sonographers to be able to participate in ROCkeTS. In real life practice, women undergo pelvic ultrasound delivered by sonographers with a range of experience and ROCkeTS endeavoured to replicate real life settings as much as possible.

USS examiners were considered QA passed if the first three scans were accurately annotated (7/8 features accurate), if not the first 10 scans were reviewed. USS examiners who failed QA received feedback and resubmitted images for QA review after reviewing online IOTA resources. The emphasis within ROCkeTS was the evaluation of risk prediction models, therefore USS examiners who had assessed the lesion correctly on subjective assessment but who had not annotated the image accurately were deemed to have failed QA. USS examiners who completed less than 10 scans for ROCkeTS were not assessed.

All tests were conducted within 3 months of recruitment, presentation and surgery/biopsy (if appropriate). Tests were conducted blind to reference standard. Study flowchart is Figure 1

Reference standard

The reference standard was histology or cytology from surgery or biopsy. . in women managed surgically. Pathology data was derived from pathology reports reported by specialist gynaecological pathologists.

For participants that did not undergo surgery or biopsy reference standard, wellbeing was ascertained using a questionnaire at 12 months. We did not stipulate a follow-up protocol for patients within the study, participants that did not have a surgery or biopsy within 3 months were managed as per local protocols. Participants that did not undergo surgery or biopsy were sent a questionnaire at 12 months to complete to ascertain health status. Research nurses also completed a questionnaire at 12 months, and we used both information to identify any patients that had been diagnosed with cancer within 12 months of recruitment to ROCkeTS. ¬¬

Outcomes

Diagnostic accuracy was assessed using sensitivity, specificity and positive/negative predictive value at different thresholds. Model performance was further assessed in terms of discrimination (c-statistic) and calibration (observed versus predicted probabilities). This approach was chosen to fully evaluate the trade-offs inherent in performance of diagnostic tests.

Primary outcome

The primary outcome was diagnostic accuracy of index tests for diagnosing OC (binary outcome), defined as primary invasive ovarian malignant neoplasms diagnosed by histology from surgery or biopsy versus benign or normal or at follow-up. Primary invasive OC was defined as ovarian, fallopian tube or primary peritoneal cancer.

Secondary outcomes

The secondary outcome was accuracy of the index tests for diagnosing OC (binary outcome) defined as: Primary invasive (OC diagnosed by surgery histology, biopsy histology or cytology alone), secondary malignant, borderline neoplasms and neoplasms of uncertain or unknown behaviour versus benign or normal. Analysis of the secondary outcome was also performed with borderlines grouped with benign and normal. In order to understand variability in test performance particularly for ultrasound models, prespecified analyses investigated diagnostic accuracy as per secondary outcome definition of OC in the subset of patients recruited in high volume centres (defined as those recruiting > 50 patients to the study) and in the subset of patients where ultrasound scan was performed by USS examiners who passed QA. We did not investigate interobserver variability at the individual sonographer level.

Sample size

The original sample size was based on performance of RMI 1 assumed to be 70% sensitive and 90% specific to detect an increase in sensitivity of 10% (to 80%) and in specificity of 5% (to 95%). Based on prevalence of 30% of OC in referred women (local audit), a sample size of 1333 provided 90% power to detect an increase in sensitivity to 80% and specificity to 95% in paired data (conservatively assuming independence of test errors). A review of the early recruit prevalence revealed a much lower prevalence of 8%. Furthermore, our systematic review on the sensitivity of models suggested that sensitivity could increase to 85%, thus a 15% difference. (12)Therefore, a sample modification was required due to prevalence, the assumed difference in sensitivity and test error correlation as many components of the alternative tests(to be compared to RMI 1 contains aspects of the RMI 1, making positive test error correlation likely.

Thus, study sample size was reset based on requiring 150 OC cases to detect a 13% difference in sensitivity from 70% to 84% with 90% power, assuming positive correlation of test error. Prevalence was monitored to ensure that target recruitment of 150 OC cases was reached before the study recruitment paused.

Missing data

Participants with missing or inconclusive reference standard results were recorded, but excluded from the primary analysis. A sensitivity analysis was done for missing index test results rather than for the reference standard. Secondary analyses were done to make the best use of the participants, resulting in exclusion of a very small percentage of participants with no reference standard, 2.3% (n=28) due to no histology, missing outcome or having a diagnostic category of other (4 patients – non diagnostic material). At sensitivity analysis, missing values for the remaining variables were imputed using the multiple imputation by chained equations (MICE) for predictors of index test combinations to avoid bias and make best use of the data, by replacing missing values with plausible values based on the distribution of the observed data (22). The methodology compensated for the uncertainty of the imputation procedure and ultimately allowed us to perform the analysis with greater power on majority of the participants. Distributions of imputed values were visually checked for comparability with the observed data.

The number of imputed datasets that were created was determined by the percentage of participants that had at least one variable missing. For instance, if 15% of individuals had at least one variable predictor missing, then 15 imputed datasets were created. If the percentage was less than 10%, then 10 imputed datasets were created. Missing or inconclusive data for reference standard was not imputed.

Imputed datasets were created by replacing missing values with simulated values from a set of imputation models constructed from all predictors and the outcome variable. Multiple imputation n was performed using the ‘mi’ package in Stata 17

Statistical analysis methods

Sensitivities, specificities, the C-index (area under the curve) and the positive and negative predictive values (PPV and NPV) of the following index tests were calculated, as compared to the reference standard: RMI 1 (Threshold 200), ROMA, ADNEX, IOTA simple rules IOTA sRisk model and CA125

were compared to the existing RMI 1 model at a threshold of 250 accounting for multiple testing with Bonferroni correction. A receiver operating characteristic (ROC) plot was created including each index test (excluding IOTA simple rules) with labels for the respective thresholds. The difference in sensitivity and specificity (and their corresponding 95% confidence intervals) was assessed using McNemar's test. The p-values were calculated using the exact McNemar test and are for the differences in sensitivities and specificities. The corresponding confidence intervals are exact binomial (asymptotic). Multiple testing was accounted for by use of the Bonferroni correction. (22, 23).

For the risk prediction models (ROMA, ADNEX, IOTA sRisk), we compared the observed outcome from histology or at 12 months follow-up with the predicted risk by creating calibration plots and assessing the calibration slope. For calibration plot, women were grouped into deciles ordered by predicted risk and the agreement between the mean predicted risk and the observed events in each decile was assessed. The value for the calibration slope should ideally be one signifying perfect agreement between the predicted probabilities and the observed probabilities. A calibration slope <1.0 would indicate that a model over-predicts while a calibration slope > 1 would indicate under prediction.We used the 'pmcalplot' command in Stata to generate the calibration plots, as recommended. (24) Asymptotic method was used to compute the confidence interval for the c-statistics.

Results

Recruitment to the postmenopausal cohort occurred from 23 hospitals across UK between 3rd July 2015 and October 2018 with follow-up ending in October 2019. Figure 1 is ROCkeTS recruitment.

The demographics and clinical characteristics of the 1,242 post-menopausal women are presented in Table 1, stratified by primary outcome definition of OC versus no OC. The median age was 65.3 (57.9-73.3) years. There were 215 (17.3%) post-menopausal women diagnosed with the primary outcome definition of OC, 197 (15.9%) diagnosed by surgery or biopsy histology, while 18 (1.4%) identified at 12 months follow up. FIGO stage of 215 participants diagnosed with OC was Stage 1 in 65 (30%), Stage II in 25 (12%), Stage III in 92 (43%), Stage IV in 16 (7%), missing in 17 (8%). 861 participants (69.3%) were diagnosed as benign or normal or absent with ovarian cancer over 12 months. Of 166 (13.4) diagnosed as Other, including missing (n=14), 58 (4.7%) had borderline neoplasm, six (0.5%) had neoplasms of uncertain or unknown behaviour, 10 (0.8%) had no histology, 22 (1.8%) had secondary malignant neoplasm, 20 (1.7%) had primary invasive malignant neoplasm where the primary cancer site was not in the ovarian and fallopian tube or primary peritoneal (therefore also secondary malignant neoplasm), 9 (0.7%) had primary invasive malignant neoplasm where the primary cancer site was in the ovarian or fallopian tube, but the method of cancer diagnosis was cytology alone or not reported, 4 (0.3%) had a diagnostic category of Other, 21 (1.7%) reported a diagnosis of non-ovarian cancer identified at 12-months follow up and two (0.2%) categorised as secondary cancer.

The secondary outcome definition of cancer included Primary invasive ovarian malignant neoplasm, secondary malignant neoplasms, borderline neoplasms, neoplasms of uncertain or unknown behaviour or diagnosed with cancer in the last 12 months and included 353 (28.4%) participants. Of the 353 women, 206 (16.6%) were diagnosed with primary invasive ovarian malignant neoplasm by surgery histology, biopsy histology, cytology or method was unknown and 18 (1.4%) were identified at the 12 months follow up. Further 42 (3.4%) women had secondary malignant neoplasm, 58 (4.7%) had borderline neoplasm and six (0.5%) had neoplasms of uncertain or unknown behaviour from the Surgery CRF. There were 21 (1.7%) participants reported with a diagnosis of non-ovarian cancer identified at 12-months follow up and two (0.2%) categorised as secondary cancer from the SAE form. Other including missing (n-14) were 28 (2.3%).

133 USS practitioners participated in ROCkeTS, 38/41 passed QA and performed 71% of scans, 92 were not assessed.

Primary outcome analysis

Data from 1,076 individuals were used to validate the index tests based on the primary outcome definition of OC. Table 2 provides estimates of the accuracy of RMI 1, ROMA, ADNEX, IOTA sRRisk model, IOTA simple rules and CA125 individually, followed by pairwise comparisons of diagnostic accuracy with the comparator test RMI 1 at a threshold of 250. Table 2

RMI 1 at 250, had sensitivity 82.9% (95% CI: 76.7 to 88.0) and specificity 87.4% (95% CI: 84.9 to 89.6). Sensitivity was highest for ADNEX at 3.0% (100.0%, 95% CI: 98.0 to 100.0), followed by ROMA at 14.4% (97.9%, 95% CI: 94.7 to 99.4), however specificities of ADNEX at 3.0% and ROMA at 14.4% were lowest, with specificities of 30.8% (95: CI: 27.5 to 34.4) and 42.4% (95% CI: 38.9 to 46.0) respectively. All index tests generally had a high NPV ranging from 95.6% to 100.0%, whereas the PPV ranged from 26.8% (ADNEX at a threshold of 3.0%, 95% CI: 23.5 to 30.3) to 69.0% (IOTA simple rules, 95% CI: 61.1 to 76.2).

The IOTA simple rules was the only index test that included inconclusive results, consisting of 226 (21.0%) participants. The c-index of the index tests at various thresholds ranged from 0.88 (IOTA sRisk model, 95% CI: 0.85 to 0.91) to 0.93 (ADNEX, 95% CI: 0.91 to 0.95). The ROC plot of index tests (excluding IOTA simple rules) is shown in Figure 2A, with thresholds labelled. The calibration plots for ROMA, ADNEX and IOTA sRisk prediction models are shown in Figure 2A, 2B. ROMA overestimated risk for the primary outcome. ADNEX and SRRisk overestimated risks above 5%, but note that these models were developed for the secondary outcome.

Pairwise comparison of test accuracy with RMI 1 at threshold of 250, accounting for multiple testing with Bonferroni correction (11 pairwise comparisons, p=0.0045 indicate statistically significant result), was available for a maximum of 980 (91.1%) participants. For the primary outcome, IOTA ADNEX at 10% was more sensitive (difference of 13.9, 95% CI: 7.6 to 20.2, p<0.001) but less specific (difference of 28.5, 95% CI: 24.7, 32.3, p<0.001) than RMI1 at a threshold of 250. Whilst ROMA at 29.9% had a comparable sensitivity (difference of 3.6, 95% CI: -1.9 to 9.1, p=0.2379) with a lower specificity (difference of 5.2, 95% CI: 2.5 to 8.0, p=0.0001).

Secondary outcome analysis

Accuracy of index tests were presented for a maximum of 1,214 (97.7%) participants for the secondary outcome definition of OC. (Table 1B) There were 353 (28.4%) post-menopausal women diagnosed with the secondary outcome definition of presence of cancer. (Table 3)

RMI 1 at 250 had sensitivity of 71.2% (95% CI: 65.8 to 76.2) and specificity of 87.4% (95% CI: 84.9 to 89.6). The sensitivity was high for ADNEX at a threshold of 3.0% (98.6%, 95% CI: 96.6 to 99.6), followed by ROMA at 14.4% (92.7%, 95% CI: 89.2 to 95.4). However, specificities of ADNEX at 3.0% and ROMA at 14.4% were lowest, with specificities of 30.8% (95: CI: 27.5 to 34.4) and 42.4% (95% CI: 38.9 to 46.0) respectively. All index tests generally had a high NPV ranging from 88.3% to 98.2%, whereas the PPV ranged from 37.1% (ADNEX at a threshold of 3.0%, 95% CI: 33.7 to 40.6) to 76.4% (IOTA simple rules, 95% CI: 69.9 to 82.0). The c-index of the index tests at various thresholds ranged from 0.84 (IOTA simple rules, 95% CI: 0.81 to 0.87) to 0.89 (ADNEX, 95% CI: 0.86 to 0.91). The ROC plot of index tests (excluding IOTA simple rules) is shown in Figure 3, with thresholds labelled. Calibration results for ROMA, ADNEX and IOTA sRisk model and plots are reported Figure 3A, 3B. Calibration appeared to have improved for all three models.

Pairwise comparison of diagnostic accuracy with RMI 1 at threshold of 250, accounting for multiple testing with Bonferroni correction (11 pairwise comparisons, p=0.0045 indicates at statistically significant result), was available for a maximum of 1,102 participants. IOTA ADNEX at 10% was more sensitive (difference of 21.1, 95% CI: 15.8 to 26.4, p<0.001) but less specific (difference of 28.5, 95% CI: 24.7, 32.3, p<0.001) than RMI1 at 250. Whilst ROMA at 29.9% had comparable sensitivity (difference of 4.1, 95% CI: -0.2 to 8.4, p=0.0614) with lower specificity (difference of 5.2, 95% CI: 2.5 to 8.0, p=0.0001).

In secondary analyses, we analysed the diagnostic accuracy of the index tests but by including borderline tumours with benign tumours or normal results. Appendix page 2-6 . We analysed diagnostic accuracy in 863 women where scans were performed by those who had passed IOTA quality assurance. Appendix pages 7-11, Finally, diagnostic accuracy in a subgroup of 840 women recruited in high volume centres (defined as recruitment of at least 50 participants) was analysed. Appendix pages 13-16. All three analyses were consistent with secondary outcome analysis. Sensitivity analysis with imputation for missing data were consistent with the main analysis, indicating findings are robust to missing data. Appendix pages 17-24.

In posthoc analyses, we compared results of both primary outcome and secondary outcome for ORADS at 10% with RMI 1 at 250. Appendix pages 25-26. In both, ORADS demonstrated comparable sensitivity to RMI 1 250 but with lower specificity. For primary outcome, compared to RMI 1, ORADS 10% had comparable sensitivity of 76.4% (95% CI: 70.1 to 82.0) and specificity of 78.3% (95% CI: 75.3 to 81.0). Similarly for the secondary outcome ORADS had comparable sensitivity of 73.2% (95% CI: 68.2 to 77.9) with specificity of 78.3% (95% CI: 75.3 to 81.0). Supplementary Tables 7,8.

Discussion

Results show that in newly presenting symptomatic postmenopausal women, three diagnostic tests, IOTA ADNEX at 3% and 10% and the ROMA test at a threshold of 14.4 (lower than manufacturer

recommended threshold of 29.9) demonstrate high sensitivity, exceeding 90%. Of these, IOTA ADNEX model at 10% had the highest specificity of 58.5%. ROMA at 29.9 achieved comparable sensitivity to RMI 1 at a threshold of 250 with lower specificity. Results are consistent across primary and secondary outcome analyses and in sensitivity analyses. Similar results were achieved in the subgroup of patients receiving USS by QA passed practitioners and in high volume centres. ORADS performed comparable to RMI in sensitivity with significantly lower specificity.

Based on superior sensitivity and limited reduction in specificity, we recommend IOTA ADNEX at 10% as new standard of care in in post menopausal women referred to hospital for suspicion of ovarian cancer, due to their higher risk of OC and because preservation of ovarian function or fertility are unlikely to be priorities mitigating the adverse consequences of unnecessary surgery in those with false positive test results. This prioritization of sensitivity over specificity was strongly supported both by our patient participant and patient advocacy representatives and policy experts in our Project oversight group.

Prioritising sensitivity over specificity increases the risk of false positives, generating anxiety for patients and unnecessary workload for health systems. We have previously identified high anxiety and distress levels for women undergoing diagnostic testing for ovarian cancer, however this is relatively lower in postmenopausal women compared to premenopausal women. (Kwong et al 2024) Reference Implementation of IOTA ADNEX into clinical care must consider mitigating the consequences of false positive testing to the individual and health system by, for e.g. incorporating MRI as an additional test for women scored at IOTA ADNEX 1-50%. It is important to recognise that some women who test as false positive will opt for surgery to manage symptoms of a pelvic mass regardless of test results.

A health economic analysis of adopting new diagnostic standards, such as IOTA ADNEX at the 10% threshold, is underway and will offer crucial insights for health policy decision-making. The choice of threshold of 10% with higher specificity or 3% with much lower specificity will depend on health systems priorities. Our choice of 10% as recommended new standard of care diagnostic is based on the relatively large drop of specificity relative to the increase in sensitivity moving from a 10% threshold to a 3% threshold which will be reflected in a much larger number of false positives compared to the drop in false negatives.

Whilst performance of RMI1 and IOTA simple rules is consistent with previous studies, performance of ROMA, ADNEX and ORADS differ significantly. (21, 25, 26, 27, 28, 29) The specificity of IOTA ADNEX has been reported as higher in multiple studies but shows variation by centre of practice. (27) A retrospective study of over 4500 patients with USS performed predominantly by experts investigated the performance of a two step strategy with initial triage with simple descriptors followed by IOTA ADNEX to ORADS. At the 10% risk threshold, the O-RADS lexicon had 92% sensitivity (95% CI, 87%-96%) and 80% specificity (95% CI, 74%-85%), and the IOTA 2-step strategy had 91% sensitivity (95% CI, 84%-95%) and 85% specificity (95% CI, 80%-88%)(21).

However, key differences between ROCkeTS and this study exist which could explain test performance: A) differences in patient spectrum (case-mix) – 67% of ROCkeTS participants were rapid access referrals i.e the first point of referral to hospital (less selected) compared to 68%

participants from cancer centres in Timmerman study, (highly preselected). (6) B) study methodology - ROCkeTS was prospectively conducted with predefined inclusion and exclusion criteria whereas Timmerman was a retrospective study C) Test characteristics – 119/133 (89%) professionals conducting USS within ROCkeTS were Level 2 sonographers in contrast to predominantly medical experts in USS within Timmerman.

One previous study investigated performance of IOTA ADNEX in three hospitals with non-specialist sonographers; however both UK participating hospitals had previously participated in IOTA studies and were led by PIs with international reputations for excellence in USS, with one PI being an IOTA founding member. Thus, sonographers in both departments may have had access to specialist expertise not available in many NHS hospitals (30).

Histology types and surgical outcomes from patients with ovarian cancer within ROCkeTS has been described elsewhere and demonstrates that women diagnosed through symptom triggered testing have high cytoreduction rates, low volume cancer and early-stage disease. 25% of patients with high grade serous ovarian cancer were diagnosed at Stage1/2 reinforcing the importance of an accurate diagnosis in women with non-specific symptoms. (31) Recruitment to ROCkeTS was predominantly through rapid access referrals but also recruited patients who presented as emergency admissions or elective clinic presentations. Patients who present as emergencies are frequently too unwell to undergo full staging. It is likely that this is the reason for the missing stage data seen in 8% of patients with OC.

Strengths

ROCkeTS recruited only newly presenting women with symptoms, resulting in a lower prevalence of OC (17%), more early-stage cancers (42%) and a more applicable population for evaluation of risk prediction models than published literature. ROCkeTS was prospectively conducted with prespecified protocol, statistical analysis plan and sample size. Tests were conducted blinded to outcome. USS training and QA were mandated. Recruitment was conducted through research nurses across multiple sites limiting selection bias. Outcome data at 12 months follow-up for patients was ascertained robustly through information obtained directly from patients as well as research nurses. Missing data was appropriately handled. Statistical analysis was conducted independent of clinical investigators and ultrasound experts. We provide provide clarity on how perimenopausal status was handled to address the diagnostic challenges across different stages of menopause.

ROCkeTS is a pragmatic study reflecting the patient population that is referred from primary care/community practice to hospital. As such, we believe that this is a key strength of our study and reflects a relatively unselected population for assessment of diagnostic test accuracy, in contrast to published studies which reflect a highly pretested population. However, this means the patient population included in ROCkeTS are heterogenous with respect to the type and severity of symptoms, which reflects the conundrum faced in community/primary care.

Analysis carefully delineated the performance of diagnostic tests and contribution made by cancers metastatic to ovary and borderline tumours (secondary analysis) versus that made by primary ovarian cancer alone (primary analysis).

Limitations

ROCkeTS recruited a predominantly white population; results may be less applicable to diverse ethnicities. Study recruitment and follow-up was completed by October 2019, however analysis was delayed until 2023 due to post COVID challenges in data cleaning by sites and sample analysis. Internationally the only new diagnostic test for ovarian cancer introduced into clinical care over the last ten years is ORADS which has been analysed within ROCkeTS. We followed up to date guidance on the interpretation and analysis of IOTA ADNEX and other risk prediction models as recommended. (32)Despite the limitations of delay, results are still applicable for practice as ROCkeTS analyses performance of all risk prediction models/scores used in common clinical practice.

Recruitment was conducted by research nurses and delivered through the National Collaborative Research Network so it is extremely unlikely that a systematic bias exists within ROCkeTS recruitment. Appendix page 42. However, it is possible that patients with advanced stage cancer who were poorly or anxious did not enroll in the study. Fig 1 shows consort and recruitment diagram indicating 81% of screen eligible participants were recruited.

Samples were stored at -80, the stability of He4 (key component of ROMA test) in freeze-thaw cycles has been previously demonstrated; this delay is unlikely to impact the results(33). The majority (71%) of USS were performed by 38 practitioners who passed ultrasound QA. However, we observed a long tail of small numbers of scans performed by sonographers who were not QA assessed; this may contribute to the lower than expected specificity of USS. However, similar specificity was also seen in high volume recruiting centres, suggesting this may be the true specificity in this population. We were unable to assess the contribution of two ultrasound features included in the 2024 ORADS v2 update – bilocular cyst or shadowing for solid lesions as this was not collected; impact of this is uncertain (10, 18).

Whilst our manuscript discusses performance of diagnostic tests by accuracy measures, we do not present data on net benefit or clinical utility. These measures may be equally important in understanding test performance, especially in the context of influencing clinical decision making. (34) (35) Health economic analysis is underway and will be crucial to understand the broader impact of our findings.

The implications of ROCkeTS findings may vary across public and private funded health systems based on the extent of guideline compliant practice.

Conclusion

Careful consideration of risk versus benefit and patient perspectives supports prioritization of an increase in sensitivity over a limited reduction in specificity in risk prediction models for the diagnosis of OC in postmenopausal women newly presenting to hospital with abnormal tests and symptoms. Thus, we recommend IOTA ADNEX at 10% should replace RMI1 as standard of care diagnostic test for OC. ROCkeTS also demonstrates that non-expert sonographers can deliver IOTA ADNEX ultrasound model for ovarian cancer detection with excellent accuracy. Appropriate sonographer training and integrating Quality assurance is integral to implementing this in routine practice.

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Collaborators – as supplementary file

Contributors

SS, CD, SM, JD conceptualised and designed the study. SS, SJ, PS, RS-V recruited to the study with collaborators with CR, RO and LS coordinating the study, SM, JD, KS and RA analysed results from the study, BVC, DT and TB conducted ultrasound QA, training, SK, RN, UM and A G-M provided input into study design and conduct. HS provided patient perspectives throughought the study from grant application, study conduct and interpretation of results. All authors reviewed results and manuscript.

JD, RA and KS along with LS and RO have directly accessed and verified the underlying data reported in the manuscript.

All authors confirm that they had full access to all the data in the study and accept responsibility to submit for publication

Conflict of interest

SS reports a research grant from AoA diagnostics for work with samples collected in this study but not reported within this manuscript. SS reports honoraria from Astra Zeneca, Mercke and GSK and consultancy from GSK and Immunogen, all unrelated to this work.

TBo reports grants, personal fees, and travel support from Samsung Medison; travel support from Roche Diagnostics; and personal fees from GE Healthcare; all outside the submitted work. BVC and DT report consultancy work done by KU Leuven to help implementing and testing the ADNEX model in ultrasound machines by Samsung Medison and GE Healthcare, outside the submitted work. All other authors declare no competing interests. UM stock ownership awarded by University College London (UCL) until October 2021 in Abcodia. UM and AGM report research collaboration contracts with QIMR Berghofer Medical Research Institute, iLOF (intelligent Lab on Fiber), RNA Guardian, Micronoma, Mercy Bioanalytics, Synteny Biotechnology. SK reports honorary role as Ovacome charity trustee. DT, TBo and BVC are IOTA steering group members and developed the IOTA models.

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Data availability

The dataset generated and analysed during the study is available at Birmingham Clinical Trials Unit, University of Birmingham. The dataset is not publicly available but maybe obtained on request to SS, review by Project oversight group, NIHR and after fulfilling all data transfer requirements.

Research in context

Evidence before this study

We searched OVID MEDLINE, OVID EMBASE, ClinicalTrials.gov, Cochrane library and Semantic Scholar to January 2024 using search terms ROMA, IOTA ADNEX, ORADS, IOTA simple rules and RMI. We did not find any head-to-head comparisons of these tests in the same patient population against the same reference standard.

Added value of the study

ROCkeTS investigated all commonly used clinical risk prediction models in a head-to-head prospective, high quality test accuracy study using a common reference standard of histology or follow-up in a predefined patient population with clear inclusion and exclusion criteria reducing the potential for confounding and increasing the validity of the test comparisons. The majority of ultrasound (USS) in clinical practice are performed by non-medical sonographers rather than by experts, therefore we evaluated performance of USS risk prediction models when delivered mainly by Level 2 USS non-medical sonographers. USS certification in IOTA USS terminology was mandatory for participation with in-built Quality assurance. ROCkeTS recruited only newly presenting women with symptoms, predominantly recruiting from the first presentation to hospital (rapid access clinics) resulting in a lower prevalence of OC (17%), more early-stage cancers (42%) and a more applicable population for evaluation of risk prediction models than published literature.

Results of ROCkeTS demonstrate that in comparison to standard of care risk prediction model, RMI 1 at 250, three tests – IOTA ADNEX at 10% and 3% and ROMA at 14.4% consistently across all analyses demonstrate a > 10% improvement in sensitivity over RMI but all three reduce specificity, with IOTA ADNEX at 10% showing the least drop of specificity. We consulted with clinical and policy experts and cancer charity representative within our Project advisory group and our patient participant; all supported prioritisation of sensitivity over a reduction in specificity in postmenopausal women due to the prevalent risk of cancer (17%) and absence of considerations such as fertility preservation or ovarian hormone production.

ROCkETS results are consistent with published literature for the comparator test; however, results show lower than expected specificity for IOTA ADNEX model and lower sensitivity for ORADS as well as ROMA tests. This could be due to differences in spectrum of patients recruited (lower prevalence, less selected, more early-stage disease), test characteristics (USS by non-experts) or study methodology (prospective, multicentre delivered through research nurses, limiting selection bias) in ROCkeTS compared to previous studies.

Implications for evidence for policy and research.

Implementation of USS models by sonographers with appropriate training and inbuilt quality assurance is feasible and achieves high diagnostic accuracy. IOTA ADNEX model at 10% is likely to significantly improve the sensitivity of diagnosis of OC and should replace standard of care diagnostic test RMI 1 in the UK. Implementation into practice is likely to increase false positives with the potential consequent risk of unnecessary surgery. This will need to be carefully reduced by introducing additional complex imaging e.g. MRI for ADNEX risk of malignancy 10-50% to decrease burden to individuals and health systems.

Rockets reinforces the need for risk prediction models to be prospectively evaluated in the high-quality clinical trials in relevant populations prior to endorsement in guidelines and implementation in practice. Performance characteristics of ORADS needs further investigation in prospective studies. Future research will need to investigate how rapidly developing novel technologies such as Artificial intelligence, can be integrated alongside these validated models.

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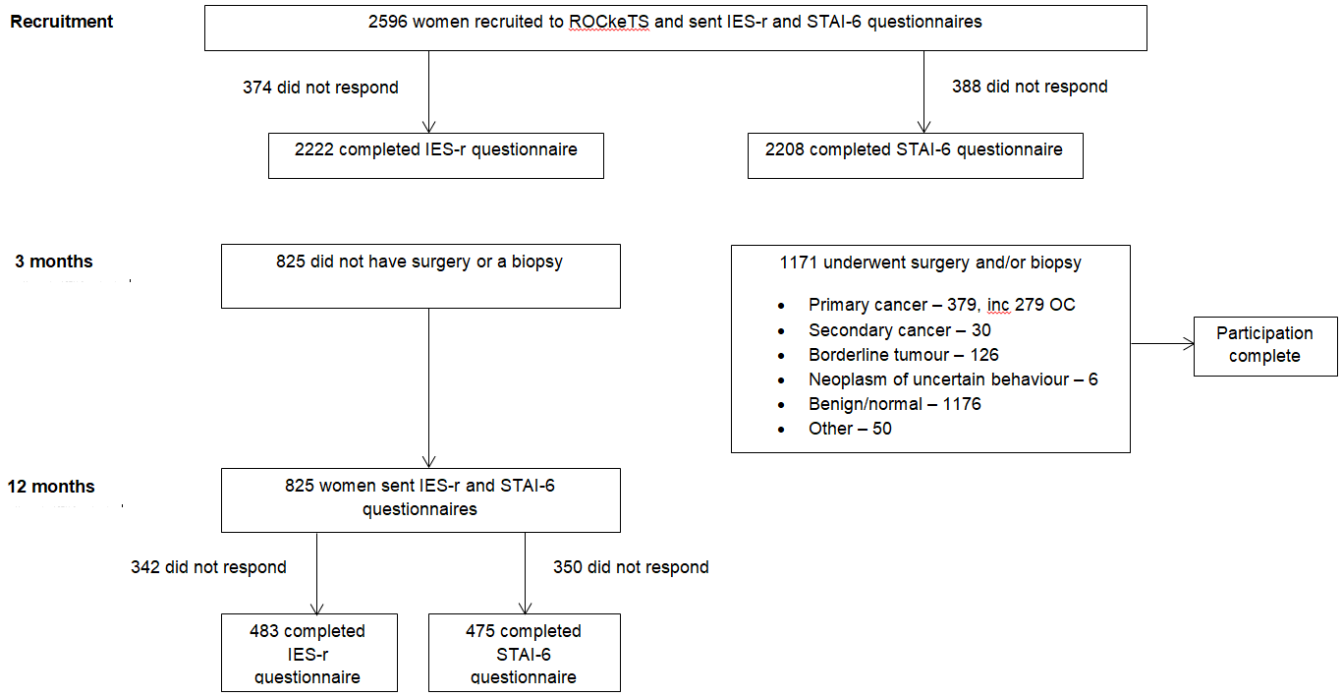
Appendix 15: Chapter 3. Recruitment flowchart

S2 Fig. Recruitment flowchart



Appendix 16: Chapter 3. Tabulation of change in STAI scores at recruitment and at 12 month follow up among 467 respondents

S1 Table. Tabulation of change in STAI scores at recruitment and at 12 month follow up among 467 respondents

		Anxiety level at 12 months n (%)			
		Mild	**Moderate**	**Severe**	**Total**
Anxiety level at recruitment	**Mild**	29 (6)	32 (7)	44 (9)	105
	Moderate	21 (4)	44 (10)	67 (14)	132
	Severe	32 (7)	60 (13)	138 (30)	230
	Total	82	136	249	467

Appendix 17: Chapter 3. Tabulation of change in IES-r scores at recruitment and 12 months follow up among 473 respondents

S2 Table. Tabulation of change in IES scores at recruitment and at 12 month follow up among 473 respondents

		Distress level at 12 months n (%)			
		Mild	Moderate	Severe	**Total**
Distress level at recruitment	Mild	159 (34)	11 (2)	50 (10)	220
	Moderate	18 (4)	3 (1)	12 (2)	33
	Severe	61 (13)	16 (3)	143 (31)	220
	Total	238	30	205	**473**

Appendix 18: Chapter 3. Prevalence of OC by age group in fast-track referrals in all postmenopausal women and in premenopausal women prior to protocol change

S3 Table. Prevalence of primary OC by age group in fast-track clinic referrals only in all postmenopausal and women and in premenopausal women prior to protocol change

Age group	n*	N**	% (95% CI)
Under 20	0	8	0 (0, 32.4)
20 to 29	0	42	0 (0, 8.4)
30 to 39	2	70	2.9 (0.8, 9.8)
40 to 49	5	186	2.7 (1.2, 6.1)
50 to 59	19	197	9.6 (6.2, 14.6)
60 to 69	24	139	17.3 (11.9, 24.4)
Over 70	21	111	18.9 (12.7, 27.2)

*n represents number of women with a true diagnosis of OC

**N represents the total number of women referred via rapid access clinics

% represents the proportion of women referred via rapid access clinics who were identified with a true diagnosis of OC

Appendix 19: Chapter 3. STATA DO/LOG files

```
*Labelling and recoding variables
label define menopausal 0 "Premenopausal" 1 "Postmenopausal", replace
recode menopausalstatus (postmenopausal=1)
label define menopausal 1 "Premenopausal" 2 "Postmenopausal", replace
recode menopausalstatus (1=0)
recode menopausalstatus (2=1)
label define menopausal 0 "Premenopausal" 1 "Postmenopausal", replace

recode age2 (min/49=0) (50/max=1), gen(age_group)
order age_group , after( age2 )
label define age 0 "under 50" 1 "over 50"
label values age_group age

recode maritalstatus 2 36 (1 4 5=0"single divorced widowed")(2 3=1"married or together")(6=2
"other"), generate(maritalstatus_r) label(maritalstatus_r) test
recode maritalstatus 2 36 (1 4 5=0 "single divorced widowed")(2 3=1 "married or together")(6=2
"other"
> ), generate(maritalstatus_r) label(maritalstatus_r) test
recode maritalstatus (1 4 5=0 "single divorced widowed")(2 3=1 "married or together")(6=2 "other"
), generate(maritalstatus_r) label(maritalstatus_r) test
shift maritalstatus_r, after maritalstatus
order maritalstatus_r, after( maritalstatus)

recode employment (1 2=0 "employed")(3=1 "self-employed")(5=2 "retired")(6=3 "unemployed")(4 7=4
"student other"), generate(employment_r) label(employment_r) test
order employment_r, after(employment)

recode ethnicity (1 2 3 4 5 6 7 15 16 11 12 13 14=0 "non-white)(8 9 10=1 "white"),
generate(ethnicity_r) label(ethnicity_r) test
recode ethnicity (1 2 3 4 5 6 7 15 16 11 12 13 14=0 "non-white")(8 9 10=1 "white"), generate(
ethnicity_r) label(ethnicity_r) test
order ethnicity_r, after(ethnicity)

recode modeofpresentation (3=0 "A&E")(2=1 "2WW")(4 5=2 "cancer unit, other specialties")(1=3
"routine GP ref"), generate(modeofpresentation_r) label(modeofpresentation_r) test
order modeofpresentation_r, after(modeofpresentation)

recode livebirths (0=0 "nulliparous")(1/4=1 "parous")(5/max=2 "grandmultip"), generate(
livebirths_r) label(livebirths_r) test
order livebirths_r, after(livebirths)

rename eversmoked_01 Neversmoked
label variable Neversmoked "never smoked"
recode Neversmoked (yes=0)
recode Neversmoked (yes=0)
label values Neversmoked .
recode Neversmoked (0=11)
order Neversmoked after( eversmoked)
order Neversmoked , before( eversmoked )
drop Neversmoked currentsmoker

**AIM 1: To establish the levels of anxiety in the referred population from the ROCkeTS dataset.
* Converting STAI-6 to STAIs and generating new variable columns
generate STAIs = STAI6/6*20

*Ascertain whether variables follow a normal distribution
swilk STAIs
swilk IES

** Table 1: details of sociodemographic characteristics of all patients
tabulate menopausalstatus
tabulate maritalstatus_r
tabulate employment_r
eabulate education_r
tabulate ethnicity_r

**Table 2: details of clinical characteristics and outcomes of participants
tabulate modeofpresentation_r
```

```
tabulate ps
tabulate eversmoked
tabulate subfertility
tabulate changeinnatureofperiods
tabulate contraception
tabulate pmb
tabulate hrt

**Table 3: Analysis of factors associated with anxiety or distress at recruitment
*Dichotomous categorical variables - Wilcoxon Rank-Sum test
tabstat STAIs , statistics( p50 p25 p75 ) by(age_group)
ranksum STAIs, by(age_group)
tabstat IES , statistics( p50 p25 p75 ) by(age_group)
ranksum IES, by(age_group)

ranksum STAIs, by( ethnicity_r )
tabstat STAIs, statistics( p50 p25 p75 ) by( ethnicity_r )
ranksum IES, by( ethnicity_r )
tabstat IES, statistics( p50 p25 p75 ) by( ethnicity_r )

tabstat STAIs, statistics( p50 p25 p75 ) by( eversmoked )
ranksum STAIs, by( eversmoked )
tabstat IES, statistics( p50 p25 p75 ) by( eversmoked )
ranksum IES, by( eversmoked )

tabstat STAIs, statistics( p50 p25 p75 ) by( subfertility )
ranksum STAIs, by( subfertility )
tabstat IES, statistics( p50 p25 p75 ) by( subfertility )
ranksum IES, by( subfertility )

ranksum STAIs, by( hxofovstimulationforsubfertility )
tabstat STAIs, statistics( p50 p25 p75 ) by( hxofovstimulationforsubfertility )
ranksum IES, by( hxofovstimulationforsubfertility )
tabstat IES, statistics( p50 p25 p75 ) by( hxofovstimulationforsubfertility )

tabstat STAIs, statistics( p50 p25 p75 ) by( changeinnatureofperiods )
ranksum STAIs, by( changeinnatureofperiods )
tabstat IES, statistics( p50 p25 p75 ) by( changeinnatureofperiods )
ranksum IES, by( changeinnatureofperiods )

ranksum STAIs, by( contraception )
tabstat STAIs, statistics( p50 p25 p75 ) by( contraception )
ranksum IES, by( contraception )
tabstat IES, statistics( p50 p25 p75 ) by( contraception )

tabstat STAIs, statistics( p50 p25 p75 ) by( pmb )
ranksum STAIs, by( pmb )
tabstat IES, statistics( p50 p25 p75 ) by( pmb )
ranksum IES, by( pmb )

ranksum STAIs, by( hrt )
tabstat STAIs, statistics( p50 p25 p75 ) by( hrt )
ranksum IES, by( hrt )
tabstat IES, statistics( p50 p25 p75 ) by( hrt )

*Categorical or ordinal variables with 3 or more groups - Kruskall-Wallis test
kwallis STAIs, by(maritalstatus_r)
tabstat STAIs, statistics( p50 p25 p75 ) by( maritalstatus_r )
kwallis IES, by(maritalstatus_r)
tabstat IES, statistics( p50 p25 p75 ) by( maritalstatus_r )

kwallis STAIs, by( employment_r )
tabstat STAIs, statistics( p50 p25 p75 ) by( employment_r )
kwallis IES, by( employment_r )
tabstat IES, statistics( p50 p25 p75 ) by( employment_r )

kwallis STAIs, by( education_r )
tabstat STAIs, statistics( p50 p25 p75 ) by( education_r )
```

```
129  kwallis IES, by( education_r )
130  tabstat IES, statistics( p50 p25 p75 ) by( education_r )
131
132  tabstat STAIs, statistics( p50 p25 p75 ) by( modeofpresentation_r )
133  kwallis STAIs, by( modeofpresentation_r )
134  tabstat IES, statistics( p50 p25 p75 ) by( modeofpresentation_r )
135  kwallis IES, by( modeofpresentation_r )
136
137  kwallis STAIs, by( ps )
138  tabstat STAIs, statistics( p50 p25 p75 ) by( ps )
139  kwallis IES, by( ps )
140  tabstat IES, statistics( p50 p25 p75 ) by( ps )
141
142  tabstat STAIs, statistics( p50 p25 p75 ) by( livebirths_r )
143  kwallis STAIs, by( livebirths_r )
144  tabstat IES, statistics( p50 p25 p75 ) by( livebirths_r )
145  kwallis IES, by( livebirths_r )
146
147  **Table 4: Calculating the confidence interval (Wilson) for each mode  of presentation
148  *Premenopausal women
149  Accident and Emergency  cii proportions 32 3, wilson
150  Rapid Access Pathway    cii proportions 363 12, wilson
151  Cancer Unit or Cross-specialties    cii proportions 77 2, wilson
152  Routine GP referral     cii proportions 76 2, wilson
153  Overall                 cii proportions 548 19, wilson
154
155  *Postmenopausal women
156  Accident and Emergency  cii proportions 67 11, wilson
157  Rapid Access Pathway    cii proportions 979 181, wilson
158  Cancer Unit or Cross-specialties    cii proportions 290 36, wilson
159  Routine GP referral     cii proportions 96 4, wilson
160  Overall                 cii proportions 1432 232, wilson
161
162  **Table S1: Calculating the confidence interval (Wilson) for each age category
163  Under 20    cii proportions 8 0, wilson
164  20 to 29    cii proportions 42 0, wilson
165  30 to 39    cii proportions 70 2, wilson
166  40 to 49    cii proportions 186 5, wilson
167  50 to 59    cii proportions 197 19, wilson
168  60 to 69    cii proportions 139 24, wilson
169  over 70     cii proportions 111 21, wilson
170
```

Appendix 20: Chapter 4. Comparison of surgical outcomes in women diagnosed with high grade tubo-ovarian cancers via the fast-track pathway in ROCkeTS study and the DOvE pilot study

Table S1. Comparison of surgical outcomes in women diagnosed with high grade tubo-ovarian cancers via the fast-track pathway in ROCkeTS study and the DOvE pilot study

	ROCkeTS	**DOvE pilot study**
Study design	Diagnostic test accuracy prospective study	Observational prospective pilot study
Country	UK	Canada
Target population	Pre- and postmenopausal women referred to hospital with symptoms of OC between 16 and 90 with abnormal CA125 and/or abnormal imaging result	50 years or older and with symptoms of OC
Recruitment dates	Jan 2015 to March 2023	May 2008 to April 2011
Context, n	Expedited testing via referral of symptomatic women to fast-track pathway by their Physician, N=1741	Facilitated testing via self-referral or referral by Physicians to satellite sites, N=1455
High grade serous tubo-ovarian cancer, n	119	9
Stage n (%)		
1 2 3 4 Unable to stage	12 (10.1) 18 ((15.1) 75 (63.1) 11 (9.2) 3 (2.5)	1&2 - 2 (22.2) 3&4 - 7 (77.8)
Cytoreduction rate n(%)		
R0 Residual <1cm Residual ≥1cm Inoperable Missing	73 (61.3) 18 (15.1) 2 (1.7) 9 (7.6) 17 (14.3)	Complete CR - 8(73)* Incomplete CR - 3(27)*

** Results for 11 women diagnosed with invasive ovarian cancer, i.e., not restricted to high grade serous ovarian cancer only*

Appendix 21: Chapter 4. Comparison of patient demographics and outcomes by mode of presentation for women with high grade serous ovarian cancer

Table S2. Comparison of patient demographics and outcomes by mode of presentation for women with high grade serous ovarian cancer

	Fast-track pathway N=119	**Emergency N=7**	**Other outpatients N=27**
Age, years* mean (S.D), p=0.031	65.0 (10.1)	55 (16.1)	66.7 (10.2)
Stage** n (%), p=0.459			
Early stage			
1	12 (10.1)	2 (28.6)	2 (7.4)
2	18 (15.1)	0 (0.0)	4 (14.8)
Late stage			
3A	16 (13.5)	1 (14.3)	1 (3.7)
3B	11 (9.2)	0 (0.0)	0 (0.0)
3C	48 (40.3)	1 (14.3)	15 (55.6)
4A	7 (5.9)	0 (0.0)	1 (3.7)
4B	4 (3.4)	2 (28.6)	2 (7.4)
Not available	3 (2.5)	1 (14.3)	2 (7.4)
Performance status** n (%), P=0.611			
0	90 (75.6)	4 (57.1)	22 (81.5)
1	22 (18.5)	3 (42.9)	2 (7.4)
2	6 (5.0)	0 (0.0)	1 (3.7)
3	0 (0.0)	0 (0.0)	1 (3.7)
Not available	1 (0.9)	0 (0.0)	1 (3.7)
Cytoreduction rate** n (%), P=0.920			
Complete	73 (61.3)	4 (57.1)	18 (66.7)
Residual <1cm	18 (15.1)	1 (14.3)	3 (11.1)
Residual ≥1cm	2 (1.7)	0 (0.0)	2 (7.4)
Inoperable	9 (7.6)	0 (0.0)	2 (7.4)
Not available	17 (14.3)	2 (28.6)	2 (7.4)

***** The ANOVA one-way test was used to calculate the p-value

**The Kruskal-Wallis H test was used to calculate the p-value

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