Original research

The avoiding late diagnosis of ovarian cancer (ALDO) project; a pilot national surveillance programme for women with pathogenic germline variants in BRCA1 and BRCA2

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ABSTRACT

Background Our study aimed to establish 'real-world' performance and cost-effectiveness of ovarian cancer (OC) surveillance in women with pathogenic germline BRCA1/2 variants who defer risk-reducing bilateral salpingo-oophorectomy (RRSO).

Methods Our study recruited 875 female BRCA1/2-heterozygotes at 13 UK centres and via an online media campaign, with 767 undergoing at least one 4-monthly surveillance test with the Risk of Ovarian Cancer Algorithm (ROCA) test. Surveillance performance was calculated with modelling of occult cancers detected at RRSO. The incremental cost-effectiveness ratio (ICER) was calculated using Markov population cohort simulation.

Results Our study identified 8 OCs during 1277 women screen years: 2 occult OCs at RRSO (both stage 1a), and 6 screen-detected; 3 of 6 (50%) were ≤stage 3a and 5 of 6 (83%) were completely surgically cytoreduced. Modelled sensitivity, specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) for OC were 87.5% (95% CI, 47.3 to 99.7), 99.9% (99.9–100), 75% (34.9–96.8) and 99.9% (99.9–100), respectively. The predicted number of quality-adjusted life years (QALY) gained by surveillance was 0.179 with an ICER cost-saving of -£102,496/QALY.

Conclusion OC surveillance for women deferring RRSO in a 'real-world' setting is feasible and demonstrates similar performance to research trials; it down-stages OC, leading to a high complete cytoreduction rate and is cost-saving in the UK National Health Service (NHS) setting. While RRSO remains recommended management, ROCA-based surveillance may be considered for female BRCA-heterozygotes who are deferring such surgery.

INTRODUCTION

Between 9–18% of all epithelial ovarian cancers (OC) occur in women with germline pathogenic variants in BRCA1/2.1 2 This increases to 20% for high-grade serous OC (HGSOC).3 BRCA1/2 variant-carriers have 44% (95% CI, 36% to 53%) and 17% (95% CI, 11% to 25%) lifetime OC risks to age 80 years, respectively.3 Consequently, they are advised to undergo risk-reducing bilateral salpingo-oophorectomy (RRSO) to prevent OC; from age 35 (BRCA1-heterozygotes) or 40 years (BRCA2-heterozygotes) onwards.5

Between 20–40% of patients with BRCA1/2-heterozygotes delay or decline RRSO.6 8 Up to 35% of women have not undergone RRSO 7 years after receiving their positive BRCA1/2 gene test result.8 9 Reasons for delaying/declining RRSO include: ongoing breast cancer treatment, addressing
breast risks first, completing families, waiting until natural menopause, the existence of comorbidities which make RSRO hazardous, fear of surgery, lack of available time, or simply not wanting surgery.6,10 Delaying/declining surgery leaves these women at risk of OC, so an effective OC surveillance programme would be an important option.

The ROCA test (CE marked and owned by Abcodia Ltd (Cambridge, UK)) is a surveillance test which has been evaluated in high-risk women through prospective trials using an intensive protocol: 4-monthly in a UK trial11 and 3-monthly in two US trials.12

The ROCA test calculates the probability of a woman having epithelial OC or fallopian tube cancer (FTC) using an algorithm which assesses the rate of change of the tumour marker CA125, to triage women into different risk categories. Abnormal ROCA test results prompt early repeat tests ± a transvaginal ultrasound scan (TVS). Surgical intervention is recommended for those with sufficiently elevated ROCA results or concerning scans.

In the UK trial,11 modelled sensitivity for asymptomatic OC/FTC was 95%. Women diagnosed with OC/FTC during 4-monthly surveillance were significantly more likely to be free of macroscopic metastatic disease outside the pelvis compared with those no longer on surveillance (95% vs 37%, respectively), a lower proportion required neoadjuvant chemotherapy (5% vs 44%, respectively), and a high proportion (95%) had no residual disease post-surgery. In most cases, complete cytoreduction during surveillance in the UK trial required little more than total abdominal hysterectomy, bilateral salpingo-oophorectomy (BSO) and omentectomy, rather than ‘ultra-radical’ surgery. While it remains speculative that such results translate into improved survival, they suggest that this form of surveillance may be a useful short-term strategy in BRCA1/2 heterozygotes who are not yet ready for RSRO.

Based on these encouraging results, the Avoiding Late Diagnosis of Ovarian Cancer (ALDO) pilot national surveillance programme for BRCA1/2-heterozygotes deferring/declining RSRO was initiated, with the ultimate objective of establishing a national OC surveillance programme for such women. Specifically, we wanted to establish whether such surveillance maintained high levels of performance in a ‘real-world’ setting (ie, high sensitivity for asymptomatic disease and earlier stage OC/FTC detection), and whether it was cost-effective.

MATERIALS AND METHODS

Recruitment

Women with pathogenic germline BRCA1/2 variants were identified through 13 Genetics Centres or Familial Cancer Clinics in England and Wales and invited to participate via letter or in clinic. The project was also advertised on online BRCA heterozygotes forums and UK OC charity websites. Recruitment ran from 4 August 2018 to 31 May 2019.

Women were eligible if aged 35–85 years, had a documented pathogenic BRCA1/2 variant, had not had both ovaries and fallopian tubes removed (women with bilateral salpingectomy only were eligible), and were able to travel to one of the ALDO project hospitals if they required TVS or gynaecological referral. BRCA variant reports were requested for all participants.

Those opting to take part, having read the participant information sheet (Supplement), completed, signed and posted consent forms to the coordinating centre (CC) using a postage-paid envelope.

Surveillance

Participants were scheduled for 4-monthly ROCA tests. The ROCA uses longitudinal serum CA125 results, age, menopausal status and lifetime risk category to calculate current probability of OC/FTC.11

Venepuncture kits were posted to participants for use in primary care. Samples were posted (in Royal Mail approved packaging for biological substances, Category B, UN3373) back to The Doctors Laboratory (London, UK) for CA-125 testing.

Menopause status was determined at each blood draw using participants’ age and answers to specific gynaecological questions on the blood sample return form (online supplemental table 1, online supplemental figures 1 and 2).

Participants’ raw CA-125 data, age and menopausal status were transmitted securely to Abcodia for processing by the ROCA, which was secured within a closed Microsoft Azure (Redmond, Washington, USA) network. Data were transmitted using a unique pseudo-anonymised identifier.

Participants were triaged according to their ROCA results (figure 1); if ‘Normal’ they continued with 4-monthly surveillance, if ‘Mildly Elevated’ they had a 6 week repeat test, if ‘Moderately Elevated’ they also had a TVS, and if ‘Significantly Elevated’ they were referred to a gynaecologist for clinical assessment (including TVS).

As an additional failsafe, any ROCA test result classified as ‘Normal’, but where the CA-125 had increased by 50% or was ≥50 U/mL was reviewed by the clinical lead (ANR) who decided whether to repeat the test 6 weeks later or continue with 4-monthly surveillance.

TVSs were organised by participating sites. If a participant was unable to attend a named site, the project team asked their primary care physician to refer them locally. TVSs were classified using the system reported in the UK Familial Ovarian Cancer Screening Study (UKFOCSS).11

Routine surveillance ran from 5 October 2018–30 November 2020. Participants with an abnormal ROCA result at their last routine test continued repeat tests as necessary until 30 April 2021. Anyone with an abnormal result was then referred to their primary care physician for CA125 tests, with clinical advice provided by the study team.

The protocol was similar to that used in UKFOCSS,11 with minor modifications (online supplemental table 2).

Participants were asked to complete baseline and follow-up questionnaires, asking about their OC surveillance knowledge, prior experience, and their experience of taking part in ALDO. Questionnaire results will be reported in a separate publication.

Surgical documentation (indication, operation notes, histopathology/cytopathology reports) was requested for all women undergoing adnexal surgery. These were reviewed by a consultant gynaecologist (ANR) and gynaecological pathologist (NS) and classified according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision, and FIGO (2018) OC staging system. A surgical complexity score was assigned using recognised criteria (online supplemental table 3).13 BRCA status was confirmed through test reports or other documentation as required.

Women were followed up via questionnaires, telephone or email. Where there was no response, we contacted their primary care physician or recruiting centres. Cancers occurring in recruited women who never underwent ALDO surveillance are reported but not included in the surveillance performance analyses.

COVID-19 impact

Routine surveillance was temporarily suspended on 23 March 2020 when the UK Government announced a nationwide


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‘lockdown’ due to the COVID-19 pandemic. Participants were asked to delay routine samples until further notice unless they were due repeat tests due to prior abnormal results. Participants requiring a TVS during this time had their results reviewed by the clinical lead (ANR), with TVS only requested in those with the most concerning ROCA results. Routine surveillance was re-instated from June-August 2020 once local site approval was confirmed.

Adherence to surveillance
Adherence to surveillance was evaluated by calculating the median number of ROCA tests/participant/year. With 4-monthly surveillance, we would expect >=3 tests/participant/year (more if any results were abnormal). As routine surveillance was suspended from 23 March 2020 due to the COVID-19 pandemic, we compared adherence before and after this date.

Statistical analysis
For participants who completed surveillance, performance analysis data were censored at 4 months after the last test. For participants who withdrew before the end of the project or died, data were censored at date of withdrawal or death, providing it occurred within 4 months of their final test. Women screen years (WSYs) were calculated from date of first test to censor date. Statistical analysis was conducted using R, version 4.0.214 and IBM SPSS Statistics version 25 (Armonk, NY). Sensitivity and Positive Predictive Value (PPV) were analysed on a per case basis to assess the performance of the entire surveillance pathway from testing to decision to operate to exclude OC/FTC. Specificity and Negative Predictive Value (NPV) were analysed on a per WSY basis. This is more conservative than analysing on a per test basis and provides data on the degree of reassurance 1 year’s negative test results provide. In addition, we conservatively included time from the penultimate rather than final ROCA test when calculating false negative (FN) WSYs for occult cancers.

As in UKFOCSS,11 in order to estimate true sensitivity, we assumed the proportion of occult cancers identified at RRSO which would have been screen-detected had women not undergone surgery would be identical to that observed in those who continued surveillance. We then used the lower CI of observed sensitivity in women who did not undergo RRSO as a conservative estimate of occult cancer detection sensitivity and rounded the predicted number of occult cancers detected to the nearest integer.

Women who underwent BSO had their surgery classified as follows: ‘RRSO’ if their last ROCA test was normal and they were asymptomatic; True-positive if they had abnormal results which prompted surgery to exclude OC/FTC and were subsequently diagnosed with invasive epithelial OC/FTC; False-positive if they had abnormal results which prompted surgery to exclude OC/FTC and were not diagnosed with invasive epithelial OC/FTC; and ‘surveillance-related’ if they had non-concerning (eg, transiently abnormal) ROCA test results which contributed to their decision to have surgery.

Prevalent OC cases were those diagnosed at the first surveillance test. Incident cases were those diagnosed subsequently. To allocate WSYs to the correct outcomes we applied the following rules: for true-positive and false-positive detection screens, the WSYs commenced with the date of the first surveillance test that led to referral and ended on the date of subsequent OC or non-OC diagnosis. WSYs prior to this were True Negative (TN). For occult cancers, we classified the WSYs commencing with the penultimate test before their RRSO as False Negative (FN). WSYs prior to this were TN. For TN cases, all WSYs were classified as TN.

Combined analysis of ROCA-based surveillance trials
To establish the overall down-staging observed with high-intensity ROCA-based surveillance in BRCA-heterozygotes, we analysed published individual OC patient data from the previous ROCA surveillance trials,11 12 combined with data from the present study, and compared OC stages with those in the BRCA-heterozygotes no longer on surveillance in UKFOCSS.11

Economic analysis
An incremental cost-effectiveness analysis of the surveillance was performed and compared with a no-surveillance (control) arm. We developed a Markov population cohort, based on a...
A hypothetical cohort of 1000 BRCA1/2-heterozygotes who were offered surveillance starting at age 35, and modelled out over their lifetime. Analysis was based on our previous trial11 and individual patient level data collected during ALDO for the surveillance arm, and from relevant literature to populate the control arm. Control women were assumed to have the choice of undertaking RRSO, or they remained disease-free, or they developed OC and entered associated therapy. The model simulation followed women from the point they undergo a gene test identifying their BRCA status, until death from OC or a competing risk, using annual cycles, which progress through a number of health states (online supplemental figure 3). The cost-effectiveness perspective adopted was the UK National Health Service (NHS).

The effectiveness measures used were life years (LYs) gained and quality adjusted life years (QALYs) gained. These are based on extrapolations of the surveillance arm and OC/FTC development in the control arm, taking into account the choices to undergo RRSO in both arms. The extrapolations were made, in the normal Markov cohort manner, through allocating transition probabilities to the population to move them through the various health states. In any given year (model cycle) a woman can decline, defer or opt for RRSO. Details of the assumptions and data used to populate the effectiveness within the model are in the online supplemental file, pages 16-21.

Only direct NHS costs covering the surveillance and control populations, and subsequent treatment costs were analysed. Resource usage was based on identification of surveillance visits, blood tests, clinic visits, surgery and follow-up clinical assessment. In addition, OC chemotherapy agents and number of cycles were based on guidance from the National Institute for Health and Care Excellence (NICE).15 All surveillance and treatments, including the use of poly-ADP ribose polymerase inhibitor (PARPi) maintenance therapy for OC/FTC, were recorded within NHS settings.

The ROCA test is currently not available in the NHS. The estimate used was the current list price of £150 per ROCA test.16 This estimate was used in the base-case analysis and subjected to sensitivity analysis to account for uncertainty surrounding this estimated value. Sensitivity analyses were also used to consider the surveillance programme ending at various ages, and detecting varying proportions of early-stage (stage 1 and 2) OC.
RESULTS

Between 5 August 2018 and 30 April 2019, 875 women returned a signed consent form. 819 (93.6%) were recruited via local genetics and familial cancer clinics and 56 (6.4%) via the online media campaign. 10 (1.1%) of the 875 women were withdrawn as ineligible, 31 (3.5%) withdrew themselves before having their first ROCA test and 67 (7.7%) were withdrawn as no blood sample was ever received (figure 2). Our analysis was on the remaining 767 women with at least one test. The median recruitment age was 40 years (range 34.5–83.3 years) (table 1). BRCA variant status was confirmed in 755 (99%) women; 339 (44.7%) BRCA1, 410 (54.1%) BRCA2, and 6 (0.8%) both BRCA1 and BRCA2. 590 women (77.2%) were pre-menopausal.

ROCA surveillance

Participants underwent 1277 WSYs (median 1.9 WSYs/woman, range 0.04–2.72 WSYs). The flow of the participants through the surveillance programme is shown in figure 2. Of the 3789 blood samples returned, 85.5% were routine, 12.4% were repeat due to an abnormal ROCA result, 1.8% were failsafe repeats (where the ROCA test was normal, but the CA125 had blood samples returned, 85.5% were routine, 12.4% were the surveillance programme is shown in figure 3). Our analysis was on the remaining 767 women with at least one test. The median recruitment age was 40 years (range 34.5–83.3 years) (table 1). BRCA variant status was confirmed in 755 (99%) women; 339 (44.7%) BRCA1, 410 (54.1%) BRCA2, and 6 (0.8%) both BRCA1 and BRCA2. 590 women (77.2%) were pre-menopausal.

ROCA results. Of the 2 false-positive surgeries, 1 had bilateral functional cysts and 1 had endometriosis.

Eight participants were diagnosed with OC/FTCs (table 2). Six were screen-detected (3 prevalent, 3 incident) and 2 were occult cancers. Additionally, 2 women who consented to take part but did not undergo surveillance developed OC/FTC (1 was diagnosed at RRSO, and 1 presented clinically). The median age at OC/FTC diagnosis was 42.5 years (range 37–60). Both occult cancers were stage 1a; 3 of the 6 (50%) screen-detected OCs were ≤stage 3a and 5 of the 6 (83%) were completely surgically cytoreduced. Three of the 6 (50%) had a CA125 <30 U/mL when first identified as abnormal by the ROCA, and 4 of the 6 (67%) had a normal TVS prior to diagnosis. OC surgery was performed within a median of 30 days (range 21–43) of referral.

All 6 OCs/FTCs (100%) in women on surveillance and who did not undergo RRSO were screen-detected (95% CI 54.1% to 100%). Hence, for modelled sensitivity, the lower confidence limit of 54.1% was used to conservatively estimate the proportion of occult cancers which would have been screen-detected had women not undergone RRSO.

Modelled sensitivity, specificity, PPV, and NPV for the detection of OC/FTC at 4 months after the last surveillance test were 87.5% (95% CI, 47.3% to 99.7%), 99.9% (95% CI 99.9 to 100%), 75% (95% CI, 34.9% to 96.8%), and 99.9% (95% CI, 99.9% to 100%), respectively.

Combined analysis of ROCA-based high-risk surveillance trials

Figure 3 compares the stages at which OCs were detected (in BRCA-heterozygotes only) across this and previous ROCA-based surveillance trials, and compares them to the women diagnosed more than 1 year after their last screen on UKFOCSS.15 This shows a significant reduction in the stage at diagnosis of incident screen-detected cases with 47% being ≤stage 3a (p = <0.05).

Economic results

The lifetime cost for a patient in the control arm is calculated at £220 677 compared with £202 337 in the surveillance arm (table 3). The Markov model estimated the number of LYs gained by the surveillance programme were 0.046; QALYs gained were 0.179. Consequently, the ROCA surveillance arm provides a health benefit at lower cost and is cost-saving for the base-case analysis; the ICER is estimated to be £102 496 saved per QALY gained.

We performed various univariate sensitivity analyses. First, we established a threshold ROCA price where the ROCA surveillance arm would no longer be considered cost-saving. This threshold price was established at £585, making the ICER for the ROCA surveillance arm £987 per QALY, which is still highly cost-effective, given current NHS England guidance.17 Similarly, if surveillance was stopped at age 70, 75 or 80 years it remained cost-saving. In addition, surveillance remained cost-saving at any proportion of early-stage (stage 1 and 2) OC detection >11.5%.

Table 1 Characteristics of the eligible participants on surveillance.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All n=764</th>
<th>BRCA1 n=339</th>
<th>BRCA2 n=410</th>
<th>BRCA1&amp;2 n=6</th>
<th>BRCA variant unknown* n=9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at recruitment (years)</td>
<td>40.0</td>
<td>39.4</td>
<td>40.8</td>
<td>44.8</td>
<td>36.5</td>
</tr>
<tr>
<td>(range)</td>
<td>(34.5–83.3)</td>
<td>(35.4–81.4)</td>
<td>(35.1–83.3)</td>
<td>(36.1–63.4)</td>
<td>(35.2–40.1)</td>
</tr>
<tr>
<td>Number Premenopausal (%)</td>
<td>590 (77.2%)</td>
<td>269 (79.4%)</td>
<td>306 (74.6%)</td>
<td>3 (50%)</td>
<td>9 (100%)</td>
</tr>
</tbody>
</table>

*Unable to obtain medical report stating which BRCA variant they had.
Table 2  Invasive ovarian and tubal cancers that occurred during surveillance.

<table>
<thead>
<tr>
<th>BRCA Variant</th>
<th>Age range at diagnosis (yr)</th>
<th>Cancer site and histotype FIGO stage, grade</th>
<th>CA125 at start of abnormal episode / at time of surgery in occult cases (U/ml)</th>
<th>ROCA score at start of abnormal episode / at time of surgery in occult cases</th>
<th>Transvaginal ultrasound scan result</th>
<th>Interval between abnormal ROCA test and surgery (days)</th>
<th>Interval between last ALDO screen and diagnosis (screen negative cases only) (days)</th>
<th>Extent of cytoreduction</th>
<th>Surgical complexity score*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalent screen-detected cancers (n=3) For these cases, ultrasound scan result is at time of referral.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA2</td>
<td>50–54</td>
<td>C57 Serous 2a, high grade</td>
<td>20.6</td>
<td>1:689</td>
<td>Normal</td>
<td>40</td>
<td>NA</td>
<td>Complete</td>
<td>2</td>
</tr>
<tr>
<td>BRCA2</td>
<td>60–64</td>
<td>C56 Serous 3a, high grade</td>
<td>133.0</td>
<td>1:13</td>
<td>Normal</td>
<td>28</td>
<td>NA</td>
<td>Complete</td>
<td>4</td>
</tr>
<tr>
<td>BRCA1</td>
<td>45–49</td>
<td>C57 Serous 3c, high grade</td>
<td>75.6</td>
<td>1:187</td>
<td>Abnormal</td>
<td>71</td>
<td>NA</td>
<td>Incomplete (&lt;1 cm deposits on rectum and bladder)</td>
<td>5</td>
</tr>
<tr>
<td>Incident screen-detected cancers (n=3) For these cases, ultrasound scan result is at time of referral.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA1</td>
<td>40–44</td>
<td>C57 Serous 1a, high grade</td>
<td>26.5</td>
<td>1:495</td>
<td>Normal</td>
<td>30</td>
<td>NA</td>
<td>Complete</td>
<td>4</td>
</tr>
<tr>
<td>BRCA1</td>
<td>35–39</td>
<td>C56 Serous 3b, high grade</td>
<td>76.7</td>
<td>1:33</td>
<td>Abnormal</td>
<td>37</td>
<td>NA</td>
<td>Complete</td>
<td>5</td>
</tr>
<tr>
<td>BRCA 1</td>
<td>55–59</td>
<td>C56 Serous 4b, high grade</td>
<td>9.1</td>
<td>1:463</td>
<td>Normal</td>
<td>43</td>
<td>NA</td>
<td>Complete</td>
<td>7</td>
</tr>
<tr>
<td>Occult cancers diagnosed within 365 days of prior screen (n=2) For these cases, ultrasound scan result pre-RRSO is by definition normal.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA1</td>
<td>40–44</td>
<td>C57 Serous 1a, high grade</td>
<td>16.0</td>
<td>1:2509</td>
<td>Normal</td>
<td>N/A</td>
<td>39</td>
<td>Complete</td>
<td>4</td>
</tr>
<tr>
<td>BRCA1</td>
<td>40–44</td>
<td>C57 Serous 1a, high grade</td>
<td>6.2</td>
<td>1:524</td>
<td>Normal</td>
<td>N/A</td>
<td>6</td>
<td>Complete</td>
<td>4</td>
</tr>
<tr>
<td>Cancers diagnosed in participants with no surveillance (n=2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA2</td>
<td>40–44</td>
<td>C56 Serous 3c, high grade</td>
<td>N/A</td>
<td>N/A</td>
<td>Normal</td>
<td>N/A</td>
<td>N/A</td>
<td>Incomplete (deposits on hemi diaphragm and omentum)</td>
<td>≥2†</td>
</tr>
<tr>
<td>BRCA2</td>
<td>40–44</td>
<td>C56 Serous 3c, high grade</td>
<td>N/A</td>
<td>N/A</td>
<td>CT scan only: Abnormal</td>
<td>N/A</td>
<td>N/A</td>
<td>Complete</td>
<td>8</td>
</tr>
</tbody>
</table>

None of the participants diagnosed with invasive ovarian or tubal cancer had a prior salpingectomy.
C56 ovarian cancer (excluding borderline ovarian tumours in this table).
C57 fallopian tube cancer.
*Surgical complexity score according to Aletti et al.13: 1–3 low, 4–7 intermediate, >7 high.
†Participant had laparoscopic assisted vaginal hysterectomy and BSO with omental and peritoneal biopsies followed by chemotherapy. Further clinical information not available.
ALDO, Avoiding Late Diagnosis of Ovarian Cancer; BSO, Bilateral Salpingo-oophorectomy; FIGO, International Federation of Gynecology and Obstetrics; N/A, not applicable; ROCA, Risk of Ovarian Cancer Algorithm.
DISCUSSION

The ALDO project has demonstrated that OC surveillance using the ROCA test for women who defer or decline RRSO in a ‘real-world’ setting has similar performance as in research trials. It has high sensitivity for asymptomatic OC and can detect early-stage disease with resultant clinical benefit. Additionally, the economic analysis has shown this surveillance is cost-saving in the UK NHS setting.

The relatively short surveillance period on ALDO meant that half of the OCs were prevalent rather than incident. This limits the ability to down-stage OC, as prevalent cancers by definition have abnormal ROCA results at their first test; had they undergone surveillance earlier, they might have had abnormal tests before this, prompting greater down-staging. Despite this, 50% of all screen-detected and 33% of incident cancers were diagnosed at ≤stage 3a; similar to the proportion of all BRCA-associated OCs detected in UKFOCSS (33.3%) and the US trials (37.5%), and far exceeding the proportion of the cancers detected more than a year after surveillance ended on UKFOCSS (5.9%).

As expected, this down-staging resulted in a high complete cytoreduction rate at primary surgery despite generally modest levels of surgical effort being required and no patients needing neoadjuvant chemotherapy. This is in keeping with the results of UKFOCSS and the US ROCA trials.

The short 30-day median referral to OC surgery interval was substantially better than that seen in UKFOCSS (82 days). This likely reflects a combination of rigorous clinical governance by the CC and a better understanding among clinicians and participants of the significance of abnormal ROCA results even with a CA125 <30 U/mL and a normal TVS; 50% of the screen-detected OCs had a CA125 <30 U/mL when first flagged abnormal by the ROCA, and 67% had a normal TVS. Additionally, 1 of 6 surveillance-detected cancers had their first repeat test brought forward by a few weeks as a result of the rigorous failsafe procedures, emphasising their utility. Unlike in clinically-detected OC, none of the cases in ALDO or the high-risk ROCA trials presented to the Emergency Room as a first OC presentation while on surveillance. We also observed high adherence to surveillance in this real-world setting, despite the impact of the COVID-19 pandemic, emphasising women’s desire for the service.

Limitations of this project include the relatively small number of cancers occurring, as would be expected on this short duration pilot implementation programme. However, the proportion of stage 1 and 2 OCs in ALDO (33%) was similar to that observed in UKFOCSS (33%) and the US ROCA trials, suggesting a consistent down-staging effect likely to be replicated in larger/longer programmes. In addition, due to financial and logistical constraints, we were not able to conduct long-term follow-up or cancer registry flagging. However, given that in UKFOCSS no interval OCs occurred nor presented clinically within a year of surveillance ending, it is unlikely in the smaller ALDO study that we would have observed any such cases had follow-up continued for longer.

Figure 3 Proportion of ovarian cancer (OC) detection at >stage 3a in BRCA-carriers among women in ALDO, UKFOCSS and the US ROCA-based surveillance trials combined, compared with women in UKFOCSS diagnosed >1 year post-surveillance. Error bars denote 95% confidence intervals. OC, ovarian cancer.
Finally, UKCTOCS utilised annual screening, whereas ALDO and the high-risk OC trials all used intensive (three or 4-monthly) surveillance, which would be expected to generate a greater downstaging effect in a fast-growing tumour such as HGSOC. For all the above reasons, directly extrapolating the UKCTOCS results to a high-risk population is difficult. However, lack of randomisation precludes assessment of potential survival benefit in the high-risk studies.11 12

We have shown that ROCA-based surveillance is cost-effective based on the NICE threshold for a screening programme (£20k/QALY), and is cost-saving in the UK NHS setting. This remains true with various sensitivity analyses, and if the ROCA test price is increased up to £585. Our Markov model is based on extensive use of the literature to construct a comparable control population and is thus open to obvious limitations. As such, the cost-effectiveness results, while relatively robust, need to be considered indicative rather than authoritative. In addition, if future OC treatment trials demonstrate a benefit for PARPi for early-stage disease, this could impact the cost-effectiveness.

There are a number of ongoing trials17–20 looking at risk-reducing salpingectomy with delayed oophorectomy as a less morbid way to prevent OC. However, the safety and efficacy of this approach has yet to be determined. Even if it demonstrates a high level of protection, it may be reasonable to consider providing post-salpingectomy surveillance until such time as completion bilateral oophorectomy has been performed.

Given that 4-monthly surveillance appears to consistently downstage OC, is associated with a high surgical cytoreduction rate at relatively low levels of surgical complexity, and reduces the need for neoadjuvant chemotherapy, we feel that this form of surveillance can be offered to BRCA-heterozygotes aged ≥35 years following informed consent, until they are prepared to undergo RRSO. Such surveillance should be viewed strictly as a short-term option only, as unlike RRSO it cannot prevent OC; women undergoing such surveillance should be counselled extensively about its limitations, and that delaying RRSO indefinitely could result in diagnosis with an incurable OC.

Table 3 Cost-effectiveness analysis results.

<table>
<thead>
<tr>
<th>Cost</th>
<th>QALYs</th>
<th>Cost difference</th>
<th>QALY difference</th>
<th>ICER</th>
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<tr>
<td>Base-case analysis</td>
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<td>ROCA price = £150</td>
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<td>Sensitivity analyses</td>
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<tr>
<td>Impact of ROCA price</td>
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<tr>
<td>Threshold analysis ROCA price = £585</td>
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<tr>
<td>Surveillance</td>
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<td>£177 0.179</td>
<td>£987</td>
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<td>Impact of surveillance duration</td>
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<tr>
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<td>Impact of proportion of early-stage (stages 1 and 2) ovarian cancer detection in ALDO</td>
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<tr>
<td>Probability of early cancer detection reduced by 10% from 33% base-case to 22%</td>
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<td>Probability of early cancer detection set at 11.5% (vs 33.3% at base-case)</td>
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<td>£103 0.106</td>
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<td>ALDO, Avoiding Late Diagnosis of Ovarian Cancer; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; ROCA, Risk of Ovarian Cancer Algorithm.</td>
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</table>

As with UKFOCSS, ALDO was not a randomised study and therefore was not able to assess the impact on survival. A recent prospective study18 looking at survival according to mode of OC detection in BRCA1 carriers found poor OC-specific 10-year survival (29.7%) in those detected by ultrasound surveillance. However, this study did not use the ROCA test, and ultrasound has not been found to downstage OC in the general population.19

The performance of annual ROCA tests for OC screening in the general population aged ≥50 years was reported in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS).19 Disappointingly, there was no reduction in mortality in this large randomised controlled trial, despite significant downstaging. However, these findings should not be a reason to deny women with a germline pathogenic BRCA1/2 variant ROCA-based surveillance. The inclusion criteria for UKCTOCS meant that very few participants would have inadvertently been BRCA-heterozygotes. In addition, the proportion of OCs which were HGSOC was lower in UKCTOCS (66.3% vs 100% in ALDO). Women with a germline BRCA variant have been shown to have a better 5-year survival from HGSOC compared with sporadic HGSOC,20 21 indicating inherent biological differences between these groups.
Supplemental material

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