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.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Not all women with pathogenic germline *BRCA1/BRCA2* alterations are willing to undergo pre-menopausal bilateral salpingo-oophorectomy to prevent ovarian cancer (OC). In clinical trials, OC surveillance using the Risk of Ovarian Cancer Algorithm (ROCA) test in such women results in earlier stage at OC diagnosis and potential clinical benefits compared with no surveillance. It is not known if this approach can succeed in a 'real world' setting or if it is cost-effective.

WHAT THIS STUDY ADDS

⇒ Surveillance performance was maintained in a 'real world' setting and appeared cost-saving when compared with a policy of no surveillance.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ ROCA-based OC surveillance can be considered for women with pathogenic germline *BRCA1/BRCA2* alterations who decline risk-reducing 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.[4] 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 RRSO 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 trial[11] 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 RRSO.

Based on these encouraging results, the Avoiding Late Diagnosis of Ovarian Cancer (ALDO) pilot national surveillance programme for *BRCA1/2*-heterozygotes deferring/declining RRSO 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 ≥50U/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
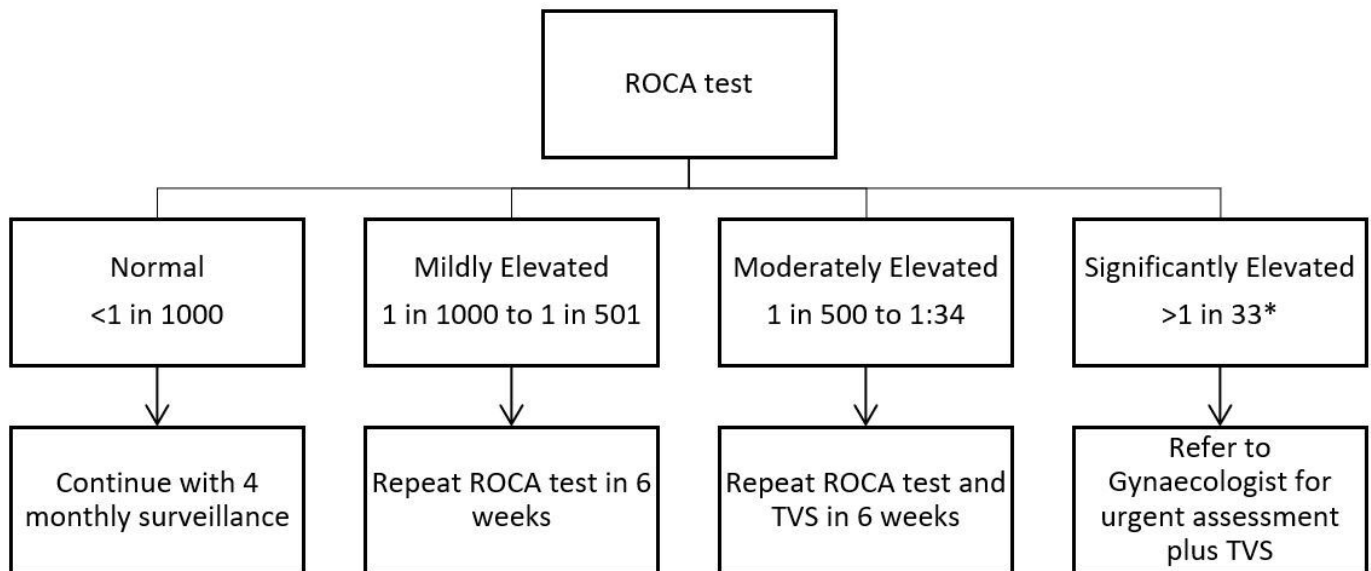
Figure 1 Triage of participants according to ROCA result categories. *NICE (National Institute for Health and Care Excellence) threshold for referral for suspected cancer. ROCA, Risk of Ovarian Cancer Algorithm; TVS, Transvaginal ultrasound scan.

'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 4.0.2[14] 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
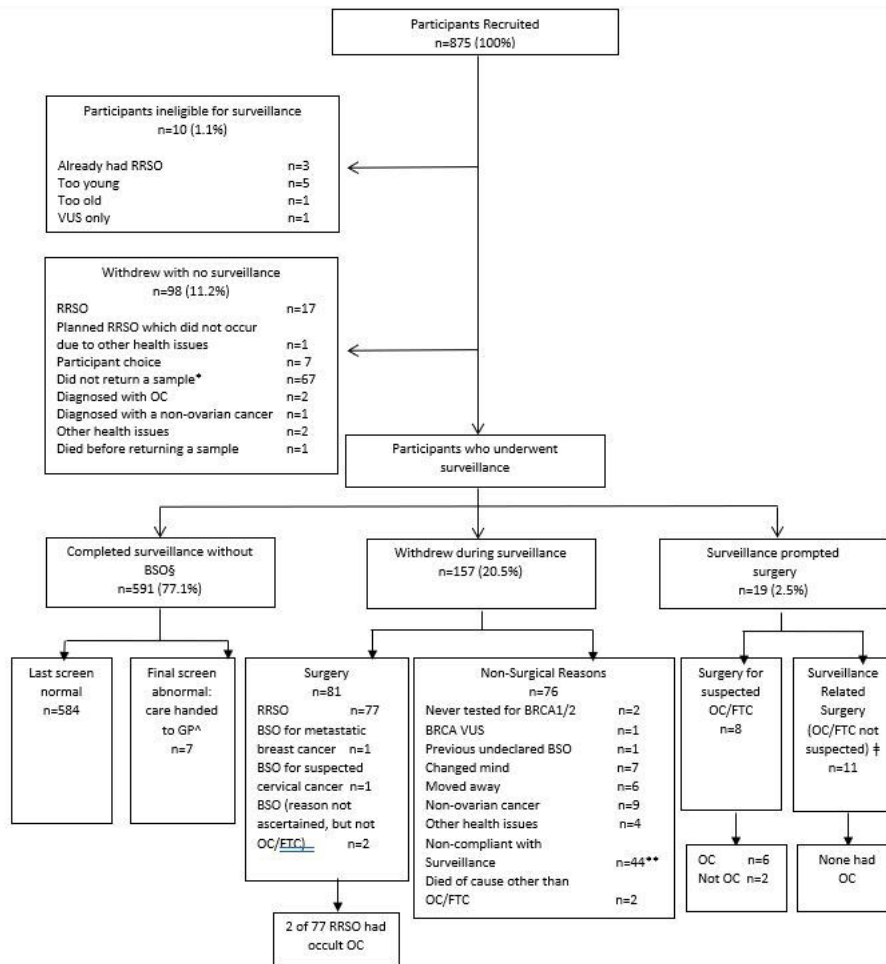
Figure 2 Consort diagram showing flow of participants through the surveillance programme. Percentages refer to the proportion of the total in preceding boxes. *Reasons for not returning sample in online supplemental table 5. §Includes four participants who had bilateral salpingectomies as part of the PROTECTOR trial (http://protector.org.uk/).[23] ∧Five were normal on repeat testing, 1 was referred for additional repeat testing which returned to normal, 1 was referred for further investigations which did not show anything abnormal. **26/44 have not had RRSO or OC, 18/44 lost to follow-up. ‡Includes a participant who underwent bilateral salpingectomy only on the protector trial. RRSO, risk-reducing bilateral salpingo-oophorectomy; VUS, variant of uncertain significance; OC, ovarian cancer; FTC, fallopian tube cancer; BSO, bilateral salpingo-oophorectomy; GP, general practitioner (primary care physician).

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 trial[11] 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 OC/FTC detection in the surveillance arm and OC/FTC development in the control arm, taking into account the choice 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.

Table 1 Characteristics of the eligible participants on surveillance.

	All n=764	BRCA1 n=339	BRCA2 n=410	BRCA1&2 n=6	BRCA variant unknown* n=9
Median age at recruitment *Years* (range)	40.0 (34.5–83.3)	39.4 (35.4–81.4)	40.8 (35.1–83.3)	44.8 (36.1–63.4)	36.5 (35.2–40.1)
Number Premenopausal (%)	590 (77.2%)	269 (79.4%)	306 (74.6%)	3 (50%)	9 (100%)

*Unable to obtain medical report stating which *BRCA* variant they had.

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 increased by ≥50% or was ≥50 u/mL), and 0.3% were discarded as the sample either arrived too late, was of insufficient quantity, or was returned in an incorrect blood tube. Outcomes of women undergoing failsafe repeat testing are shown in online supplemental figure 4.

Outcomes of women undergoing TVS are shown in online supplemental figure 5; 114 TVSs were requested in 104 women (14%). One participant was diagnosed with a non-ovarian cancer. Two of the TVSs were abnormal; one prevalent FTC (Stage 3c) and one incident OC (Stage 3b).

We referred 22 (2.8%) participants to a gynaecologist for clinical assessment, 8 underwent screen-positive surgery, 9 returned to routine surveillance, 3 were diagnosed with non-ovarian cancer (two metastatic breast cancer; one pancreatic cancer), 1 was referred to her primary care physician for a repeat CA-125 (which was normal) as surveillance had ended and 1 was placed on the waiting list for BSO (investigations were not concerning and surveillance had ended).

Overall, 3772 eligible samples were returned during 1277 WSYs (median 2.95 samples/participant/year). A total of 91.8% of requested samples were returned; 92.8% before the first UK COVID-19 lockdown, 83.2% subsequently. 2929 samples were taken during 841 WSYs (median 3.5 samples/participant/year) pre-lockdown, 843 samples were taken during 436 WSYs (median 1.9 samples/participant/year) subsequently; a reduction of 54%. Reasons for non-compliance are shown in online supplemental table 5. We found 590 (15.6%) ROCA samples were abnormal.

Overall, 19 of 767 women (2.5%) underwent surveillance-prompted surgery; 6 were screen-detected OC/FTCs (3 incident and three prevalent), 2 underwent false-positive surgery, and 11 had surveillance-related surgery (BSO or salpingectomy) which may have been due to transiently high non-concerning abnormal 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.[11] 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 2 Invasive ovarian and tubal cancers that occurred during surveillance.

BRCA Variant	Age range at diagnosis (yr)	Cancer site and histotype	FIGO stage, grade	CA125 at start of abnormal episode / at time of surgery in occult cases (U/ml)	ROCA score at start of abnormal episode / at time of surgery of occult cases	Transvaginal ultrasound scan result	Interval between abnormal ROCA test and surgery (days)	Interval between last ALDO screen and diagnosis (screen negative cases only) (days)	Extent of cytoreduction	Surgical complexity score*
Prevalent screen-detected cancers (n=3) For these cases, ultrasound scan result is at time of referral.										
BRCA2	50–54	C57 Serous	2a, high grade	20.6	1:589	Normal	40	NA	Complete	2
BRCA2	60–64	C56 Serous	3aii, high grade	133.0	1:13	Normal	28	NA	Complete	4
BRCA1	45–49	C57 Serous	3c, high grade	75.6	1:187	Abnormal	71	NA	Incomplete (<1 cm deposits on rectum and bladder)	5
Incident screen-detected cancers (n=3) For these cases, ultrasound scan result is at time of referral.										
BRCA1	40–44	C57 serous	1a, high grade	26.5	1:495	Normal	30	NA	Complete	4
BRCA1	35–39	C56 Serous	3b, high grade	76.7	1:33	Abnormal	37	NA	Complete	5
BRCA 1	55–59	C56 Serous	4b, high grade	9.1	1:463	Normal	43	NA	Complete	7
Occult cancers diagnosed within 365 days of prior screen (n=2) For these cases, ultrasound scan result pre-RRSO is by definition normal.										
BRCA1	40–44	C57 Serous	1a, high grade	16.0	1:2509	Normal	N/A	39	Complete	4
BRCA1	40–44	C57 Serous	1a, high grade	6.2	1:5324	Normal	N/A	6	Complete	4
Cancers diagnosed in participants with no surveillance (n=2)										
BRCA2	40–44	C56 Serous	3c, high grade	N/A	N/A	Normal	N/A	N/A	Incomplete (deposits on hemi diaphragm and omentum)	≥2†
BRCA2	40–44	C56 Serous	3c, high grade	N/A	N/A	CT scan only: Abnormal	N/A	N/A	Complete	8

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.
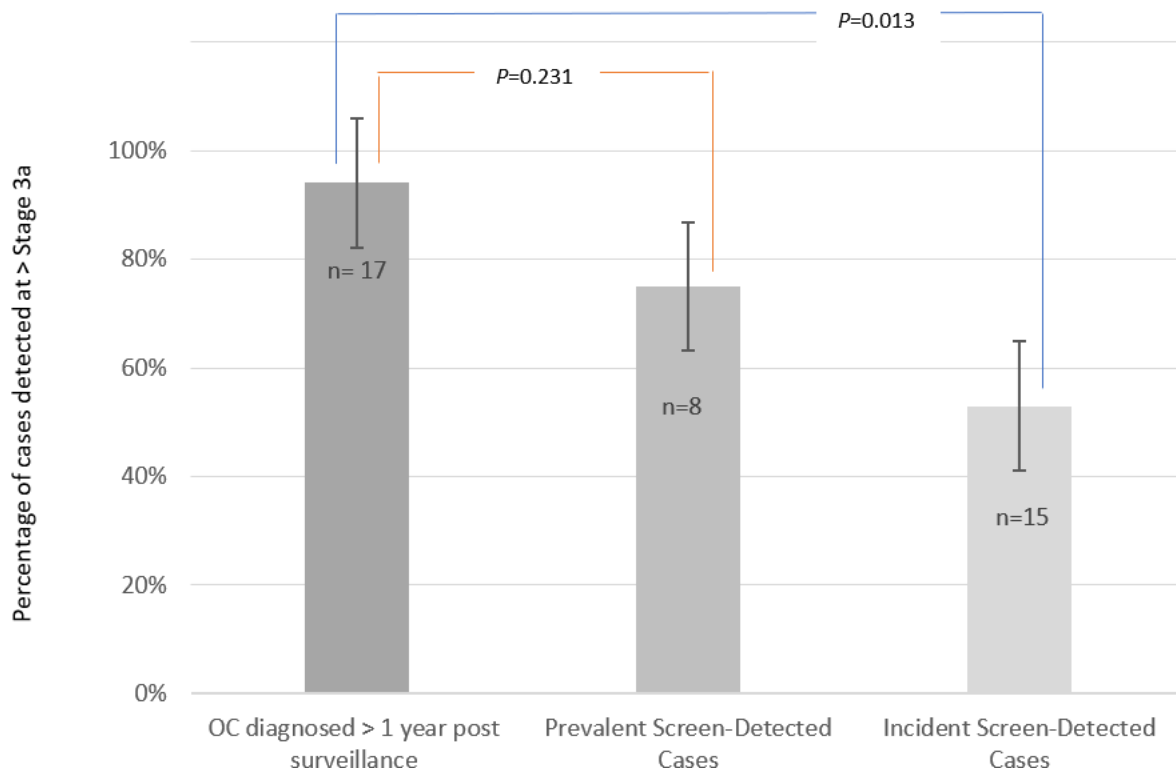
Figure 3 Proportion of ovarian cancer (OC) detection at >stage 3a in *BRCA*-carriers among women in ALDO, UKFOCSS[11] and the US[12] ROCA-based surveillance trials combined, compared with women in UKFOCSS diagnosed >1 year post-surveillance. Error bars denote 95% confidence intervals. OC, ovarian cancer.

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%)[11] and the US trials (37.5%),[12] and far exceeding the proportion of the cancers detected more than a year after surveillance ended on UKFOCSS (5.9%).[11] 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[11] and the US ROCA trials.[12]

The short 30-day median referral to OC surgery interval was substantially better than that seen in UKFOCSS (82 days).[11] 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[11] (33%) and the US[12] (37.5%) 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[11] 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.

Table 3 Cost-effectiveness analysis results.

	Cost	QALYs	Cost difference	QALY difference	ICER
Base-case analysis					
ROCA price = £150					
Control	£220 677	31.4291			
Surveillance	£202 337	31.6641	-£18 340	0.179	-£102 496
Sensitivity analyses					
Impact of ROCA price					
Threshold analysis ROCA price = £585					
Control	£220 677	31.4291			
Surveillance	£220 854	31.6641	£177	0.179	£987
Impact of surveillance duration					
Surveillance stops at age 80 years					
Control	£220 677	31.4291			
Surveillance	£201 968	31.6069	-£18 709	0.178	-£104 854
Surveillance stops at age 75 years					
Control	£220 677	31.4291			
Surveillance	£201 768	31.6069	-£ 18 910	0.178	-£106 326
Surveillance stops at age 70 years					
Control	£220 677	31.4291			
Surveillance	£201 583	31.6059	-£19 095	0.177	-£107 951
Surveillance stops at age 50 years					
Control	£220 677	31.4291			
Surveillance	£209 063	31.5759	-£11 614	0.147	-£79 086
Impact of proportion of early-stage (stages 1 and 2) ovarian cancer detection in ALDO					
Probability of early cancer detection reduced by 10% from 33% base-case to 22%					
Control	£220 677	31.4291			
Surveillance	£210 797	31.5744	-£9880	0.145	-£67 976
Probability of early cancer detection increased by 10% from 33% base-case to 43%					
Control	£220 677	31.4291			
Surveillance	£193 877	31.6416	-£26 800	0.213	-£126 106
Probability of early cancer detection set at 11.5% (vs 33.3% at base-case)					
Control	£220 677	31.4291			
Surveillance	£220 780	31.5348	£103	0.106	£971

ALDO, Avoiding Late Diagnosis of Ovarian Cancer; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; ROCA, Risk of Ovarian Cancer Algorithm.

As with UKFOCSS, ALDO was not a randomised study and therefore was not able to assess the impact on survival. A recent prospective study[18] 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 down-staging. 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.

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 down-staging 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 trials[22–25] 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 down-stage 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.

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THE AVOIDING LATE DIAGNOSIS OF OVARIAN CANCER (ALDO) PROJECT; A PILOT NATIONAL

SURVEILLANCE PROGRAM FOR WOMEN WITH PATHOGENIC GERMLINE VARIANTS IN *BRCA1* AND

***BRCA2*.**

Supplementary Tables, Figures and Information

Supplemental material

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PARTICIPANT INFORMATION SHEET

Project title: Avoiding Late Diagnosis of Ovarian Cancer (ALDO)

You are being invited to take part in the ALDO project, a one year NHS pilot scheme offering surveillance for ovarian cancer using the ROCA Test. This service is available for women like you, who are at high risk of developing ovarian cancer, and who are unable to or have not yet decided to have their ovaries removed (risk-reducing surgery).

Before you make your decision, it is important for you to understand why this project is being done and what it will involve. Please take your time to read the following information carefully. You may want to talk to your family or friends before taking part.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether you want to take part or not.

What is the purpose of the project?

Women who carry a mutation in the BRCA1 and or BRCA2 gene are at a high risk of developing ovarian cancer. The only way to prevent ovarian cancer is to have risk-reducing surgery (having your ovaries and fallopian tubes removed). However many women delay having surgery for a number of reasons such as wanting to complete their family, avoid early menopause and associated symptoms / problems or because they have other significant health problems which make surgery too risky.

For women who do delay having surgery, surveillance with a 4 monthly blood test could be a reassuring option until they are ready for surgery. Routine surveillance with the ROCA Test does not prevent ovarian cancer, but it does detect the cancer at an earlier stage than if no surveillance is done. The aim of this project is to test surveillance within the NHS and gather evidence to help the NHS decide whether this screening should be adopted as standard practice.

Why have I been invited to take part?

You have been invited to take part because you carry a mutation in the BRCA1 or BRCA2 gene, and as far as we are aware, you have not yet decided to have surgery to remove your ovaries.

Do I have to take part?

It is up to you whether you want to take part in this project. Whatever your decision, the care you currently receive will remain the same. If you agree to this now, you can stop taking part at any time and you don't have to give a reason.

If you decide to have risk-reducing surgery at any time during the project, you can continue with the surveillance until your surgery date.

What will taking part involve?

If you decide to take part, you will have a blood test taken every 4 months. You will be sent a blood taking pack to take to your GP. Once the blood has been taken, you need to post it back to us for analysis in our laboratory. We will supply the pre-paid envelope for this purpose.

Your blood will be tested for CA-125, a protein which increases in cases of ovarian cancer. The result of the CA-125 is then analysed by the ROCA Test, which tells us how likely it is that you currently have an ovarian cancer. The ROCA Test calculates your risk, by looking at your age, your menopause status and previous CA-125 levels if you have any.

Your result will be classified as one of the following:

- Normal
- Mildly Elevated (your current risk of having ovarian cancer is between 1 in a 1000 and 1 in 501)
- Moderately Elevated (your current risk of having ovarian cancer is between 1 in 500 to 1 in 34)
- Significantly Elevated (your current risk of having ovarian cancer is greater than 1 in 33)

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You will receive the results within 7 days of the sample reaching the laboratory. In most cases, an elevated result does not mean that you have ovarian cancer, but will mean that you need a repeat blood test and possibly some other investigations such as a scan of your ovaries (done using a small probe placed inside the vagina). If you do need a scan or other investigations you will need to attend one of the following hospitals, depending on where you live: UCLH (University College London Hospital), Barts Hospital London, St George's Hospital London, St Mary's Hospital Manchester, Liverpool Women's Hospital, Princess Ann Hospital, Southampton or Birmingham City Hospital. We will tell you which hospital you will be seen at.

Any results requiring scans and/or hospital appointments will be shared with you, your GP, and the local ALDO project gynaecologist with responsibility for your surveillance.

The surveillance will last for 1 year and after that you will need to discuss your options with your local genetics team or gynaecologist as appropriate.

We will also ask you to complete 2 short questionnaires, one at the start of the project and one at the end. These questionnaires are to find out your views on surveillance.

During the 18 months after the surveillance has ended we may contact you, with a questionnaire and to tell you about other research projects which you may be interested in. We will only do this if you have provided consent for this.

What are the benefits?

This ROCA Test has been tested successfully in several clinical trials over the past 15 years involving over 200,000 women.

In the UK Familial Ovarian Cancer Screening Study (UKFOCSS), screening was offered to women with a strong family history of ovarian or breast cancer, many of whom carried BRCA mutations. Women diagnosed with cancer as a result of screening had less advanced cancers compared to those who presented with symptoms after the end of screening. As a result, their surgery was less complex. Additionally the proportion of women who had all of their tumours removed was very high, which is important in terms of predicting a better outcome.

By taking part in this surveillance you will be monitored closely which you may find reassuring.

What are the limitations?

- The ROCA test will not prevent you from getting ovarian cancer, only risk-reducing surgery can do that.
- The ROCA Test may not detect all women with ovarian cancer. Therefore, it is very important to remain aware of the symptoms of ovarian cancer and speak with your doctor if you are concerned. You can find the symptoms listed at the end of this document.
- If your ROCA Test is elevated, then it will need to be repeated and in some circumstances, other tests (e.g. an ultrasound scan of your ovaries, or an MRI or CT scan) may be needed to help the doctor decide whether surgery is necessary.
- An elevated ROCA Test result does not mean you definitely have ovarian cancer. Your ROCA score could be elevated due to other medical problems. Some women might have a naturally high level of CA-125 which causes a temporary elevated ROCA result until the algorithm learns what your normal level of CA-125 is.
- Although there is evidence that more early stage ovarian cancers can be detected in women who undergo surveillance using the ROCA Test, many women will still be diagnosed after the cancer has spread, when prognosis may be poor.
- Surveillance with the ROCA Test has not yet definitively been shown to save lives. The latest report published in the Lancet[2] provides evidence which some have interpreted as encouraging but this will be clearer when there is longer follow up and a further publication, likely in 2019.

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- Ovarian cancer surveillance using the ROCA Test may create anxiety in some women if there are elevated results even when no cancer is present. In some women, these results will lead to surgery even when no cancer is present and occasionally the surgery will cause complications. All women undergoing surveillance should understand these risks.

What are the risks?

In addition to the above limitations, you may experience some bruising from having blood samples taken. If your ROCA scores are moderately or significantly elevated, you will be required to attend a named hospital for a transvaginal ultrasound scan. Some women may find this procedure uncomfortable.

Who is organising and funding this project?

The project was conceived as part of the national Cancer Vanguard's challenge to industry in 2017, to work with the NHS on projects to improve the early diagnosis of cancer. UCLH Cancer Collaborative is leading the project on behalf of its two partners in the former Cancer Vanguard – Greater Manchester Cancer Vanguard Innovation and RM Partners. Abcodia is a private company dedicated to improving early cancer diagnosis. They own the rights to the ROCA Test and are funding this project.

What will happen to my blood samples?

Your blood samples will be analysed in the laboratories used by UCLH (run by Health Services Laboratories (HSL)). The blood samples will be labelled with your initials, date of birth and study ID number. Your blood sample will be stored for 3 months before being destroyed.

If you agree to your blood samples being used for future ethically approved research projects, including projects run by commercial companies worldwide, your samples, will be stored indefinitely. These samples will be stored anonymously (your initials, date of birth and study ID will be removed).

What data will you collect and who will have access to my data?

We will store a limited amount of your personal data on a secure database held on the UCLH NHS system. This will include the personal data that you submit to us on the enclosed form, your blood results over the course of the project and results of any further investigations you may need (such as scans). If you decide to have surgery at any time during the project then we will request some details about your surgery from the hospital where you are treated. At the start of the project, we will also ask your genetics centre for a copy of your BRCA test result for our records.

In order to run the ROCA Test, we will need to transfer some anonymised data outside of the NHS to another secure database. This data will include your blood results, your age and your menopause status. We will not transfer any identifiable data such as your name or address.

Only NHS staff working on this project will have access to these secure databases. Your GP and genetics team will be informed about your participation in this project and we will share any abnormal results with them, as well as a summary of your results at the end of the project.

UCLH will act as the Lead Data Controller for this project and if you consent to take part in this project, you will be asked to provide your consent to UCLH as the Lead Organisation.

Who is involved in managing my data and how will my information be kept confidential?

All data we collect on you will be stored in a secure database within the NHS.

At the end of this document you can find a list of the organisations that are involved in this project and their roles in the management of your data.

What happens to my data at the end of the project?

At the end of the project, the data that has been collected will be anonymised and an evaluation will be carried out to assess whether the project has been successful. No personally identifiable data will be used in this evaluation or be shared outside the NHS. It will not be possible to identify you or your data in the information used for the evaluation.

An anonymised copy of the data collected as part of the project will be shared with Abcodia, to support future developments in ovarian cancer surveillance. This will include the type of BRCA1 or BRCA2 mutation, ROCA test scores and CA-125 levels for each participant, and where additional investigations or surgery have been carried out it will also include information about these. It will not include your personal details, such as your name or address. It will not be possible to identify you from this information.

We will keep all of your personal data in the secure database within the NHS for 10 years after the project. This is in line with the standard practice for research studies. If the clinical team would like to use this data for any purpose other than described here for this project, then they will make contact with you to ask for your permission for this. They will not use your data without your permission.

What will happen to the results of this project?
The results of the evaluation will be shared with NICE and other NHS Clinical Commissioners so that they can assess whether this service is beneficial to NHS patients. We hope also to publish the results of the evaluation so that a wider audience can benefit from the learning from this project.

Who has reviewed this project?
This project has been reviewed and approved by an independent NHS ethics committee and by the HRA (Health Research Authority).

Who has sponsored this project?
This project is being sponsored by University College London (reference number 17/0841).

What happens next?
If you agree to take part in this surveillance project, you will need to sign the consent form and send it back to us. If we do not hear back from you, then your recruiting site may send out a reminder letter. We will then send you a blood pack to take to your GP to have your first blood test taken. We will send you the result within 7 days of receiving the blood sample.

Who can I speak to about the project?
If you have any questions about the project, then you can speak to your genetics team or you can contact the Project Manager at uclh.aldo@nhs.net or via telephone on 07773572706.
You can also speak to your local hospital PALS service on [insert tel no] or for more independent advice you can speak to a nurse at Cancer Research UK (CRUK) on 0808 800 4040 or via a webpage https://www.cancerresearchuk.org/about-us/contact-us/talk-to-our-nurses?wssl=1.

If you decide to take part in the project, but later decide that you do not wish to continue to take part, then you can opt out by contacting the Project Manager, as detailed above.
If you wish to exercise your rights under Data Protection Laws please contact the Project Manager, as detailed above, who will direct you appropriately.

What if there is a problem?
If you have a concern about any aspect of this project, please contact the project team who will do their best to answer your questions [contact number]. If you remain unhappy and wish to complain formally, you can do this [insert local PALS number].

What are the symptoms of ovarian cancer?
The main symptoms to look out for include:

- feeling constantly bloated
- a swollen tummy
- discomfort in your tummy or pelvic area

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- feeling full quickly when eating, or loss of appetite
- needing to pee more often or more urgently than normal

Other symptoms can include:
1. persistent indigestion or nausea
2. pain during sex
3. a change in your bowel habits
4. back pain
5. vaginal bleeding – particularly bleeding after the menopause
6. feeling tired all the time
7. unintentional weight loss

Please see your GP if:
- you've been feeling bloated most days for the last three weeks
- you have other symptoms of ovarian cancer that won't go away

Your GP can do some simple tests for ovarian cancer to see if you might have it.

If you've already seen your GP and your symptoms continue or get worse, go back to them and explain this.

Data Management

The following organisations will play a role in the management of your data as part of this project. Their role is detailed in this table:

University College London (UCL)	Lead Data Controller
UCLH	Data Processor
Health Services Laboratories (HSL)	Data Processor
Your genetics or familial cancer service, including: • North East Thames Regional Genetics service (Great Ormond Street Hospital NHS Foundation Trust) • Manchester Centre for Genomic Medicine, Saint Mary's Hospital (Manchester University NHS Foundation Trust) • Barts Health NHS Trust • Guys and St Thomas's NHS Foundation Trust • Royal Marsden NHS Foundation Trust	Data Controller

A Data Processing Agreement is in place between UCLH and Abcodia, and between UCLH and HSL to govern the appropriate management of your personal information.

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Supplementary Table 1: ALDO Menopause Questions:

1. Have you had a period in the past year?
a. If yes, date of last period
2. Have you had a hysterectomy (an operation to remove your womb)?
3. Have you had surgery to remove both your ovaries?
4. Do you have a Mirena® coil fitted?
a. If yes, is this part of Hormone Replacement Therapy (HRT)
5. Have you ever had hot flushes and/or night sweats for more than 1 month?
6. Are you taking Hormone Replacement Therapy (HRT)?

Supplementary Figure 1: Flow Chart to Determine Menopausal Status for someone who has not had a hysterectomy

This algorithm is based on the principal that 12 months' amenorrhoea in women with an intact uterus and no Mirena(trademark) intra-uterine system (IUS) *in situ* indicates probable menopause. However, in those with a prior hysterectomy, or those with an IUS, or in those with an intact uterus on HRT, amenorrhoea is an unreliable sign of menopause. Therefore, a pragmatic cut-off age of 56 yr in such women was chosen, as >80% of such women would be menopausal at this age (Shadyab et al. Ages at menarche and menopause and reproductive lifespan as predictors of exceptional longevity in women: the Women's Health Initiative. Menopause. 2017 Jan;24(1):35-44) irrespective of the above factors.

Supplementary Figure 2: Flow Chart to Determine Menopausal Status for someone who has had a hysterectomy

This algorithm is based on the principal that 12 months' amenorrhoea in women with an intact uterus and no Mirena(trademark) intra-uterine system (IUS) *in situ* indicates probable menopause. However, in those with a prior hysterectomy, or those with an IUS, or in those with an intact uterus on HRT, amenorrhoea is an unreliable sign of menopause. Therefore, a pragmatic cut-off age of 56 yr in such women was chosen, as >80% of such women would be menopausal at this age (Shadyab et al. Ages at menarche and menopause and reproductive lifespan as predictors of exceptional longevity in women: the Women's Health Initiative. Menopause. 2017 Jan;24(1):35-44) irrespective of the above factors.

Supplementary Table 2: ALDO modifications to the UKFOCSS protocol	
1	The term 'screening' was replaced by 'surveillance' in keeping with NICE guidelines for surveillance for early detection of breast cancer in high-risk women[1].
2	We did not offer annual Transvaginal ultrasound scans
3	Based on the results from UKFOCSS, the ROCA cut-offs for determining the categories for repeating surveillance tests were adjusted.
4	The risk level at which women were referred direct to gynaecology rapid access clinics (without waiting for a repeat blood test or scan) was set at 1 in 33, which is the National Institute for Health and Care Excellence risk threshold for automatic 2 week wait referral for suspected cancer.
5	Following discussions with BRCA-carriers, the terms for classifying ROCA results were changed from 'Normal', 'Low Intermediate', 'High Intermediate' and 'Elevated' to 'Normal', 'Mildly Elevated', 'Moderately Elevated' and 'Significantly Elevated', respectively.
6	CA125 samples could be analysed up to 7 days post the blood being drawn (based on a stability study which found samples remained stable during that time).
7	The algorithm to determine menopause status was improved to include women with a Mirena® intra-uterine system.

1. https://www.nice.org.uk/guidance/cg164/chapter/Recommendations#surveillance-and-strategies-for-early-detection-of-breast-cancer

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Supplementary Table 3. Surgical complexity scoring on ALDO[1]	
Procedure	**Points**
TAHBSO	1
Omentectomy	1
Pelvic lymphadenectomy	1
Paraaortic lymphadenectomy	1
Pelvic peritoneum stripping	1
Abdominal peritoneum stripping	1
Large bowel resection	2
Diaphragm stripping/resection	2
Splenectomy	2
Liver resection/s	2
Small bowel resection/s	2
Rectosigmoidectomy with anastomosis	3

1. Aletti GD et al. Relationship among surgical complexity, short-term morbidity, and overall survival in primary surgery for advanced ovarian cancer. Am J Obstet Gynecol. 2007 Dec;197(6):676.e1-7. doi: 10.1016/j.ajog.2007.10.495. PMID: 18060979. https://doi.org/10.1016/j.ajog.2007.10.495

Key

TAHBSO = total abdominal hysterectomy and bilateral salpingo-oophorectomy

To calculate total score per patient, simply add scores from individual procedures undertaken during surgery and allocate to complexity group as follows:

Total score 1-3 = low complexity

Total score 4-7 = intermediate complexity

Total score >7 = high complexity

Supplementary Figure 3: Markov model used for cost effective analysis
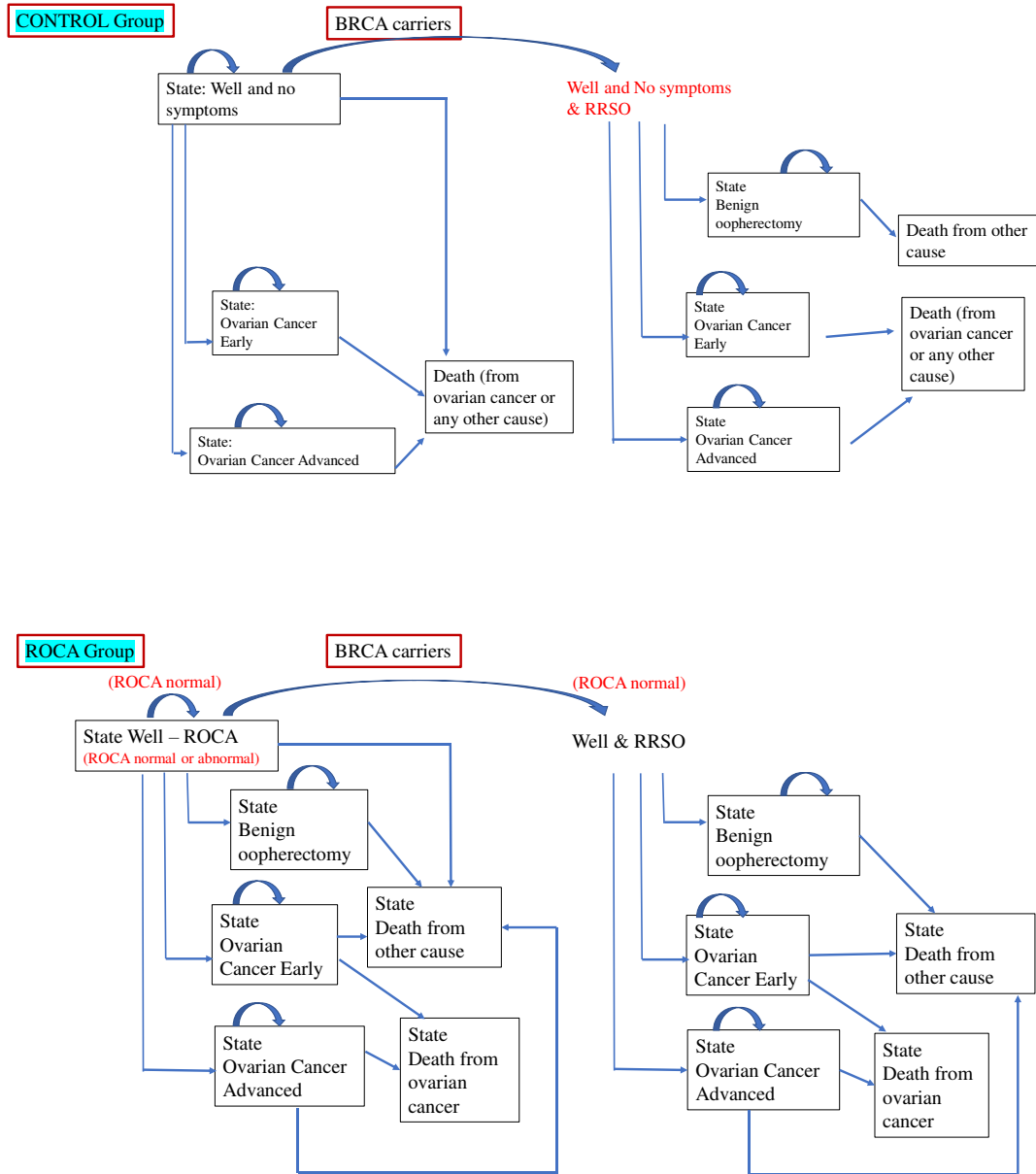
Figure 4: Results of failsafe repeat samples

```
                          ┌─────────────────────────┐
                          │ ROCA normal, but CA125   │
                          │      >50 U/ml or         │
                          │ CA125 increased by 50%   │
                          │          n=69            │
                          └────────────┬────────────┘
```

| Normalised after one repeat test n=57 (83%) | Normalised after two or more repeats n=7 (10%) | Participant was pregnant - repeat post delivery was normal n=1 | Participant had elective RRSO before test could be repeated (normal histopathology) n=1 | Subsequent ROCA was elevated n=3 |

Subsequent ROCA was elevated (n=3):

| Surveillance-related surgery (OC/FTC not suspected) (normal histopathology) ROCA-score 1:66 n=1 | False-positive surgery (ROCA-score increased to 1:44) n=1 | Surgery for suspected OC (ROCA-score increased to 1:33) n=1 |

Key

RRSO = Risk Reducing Salpingo-oophorectomy

OC = Ovarian Cancer

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Figure 5: Outcomes of scans done for moderately elevated ROCA results
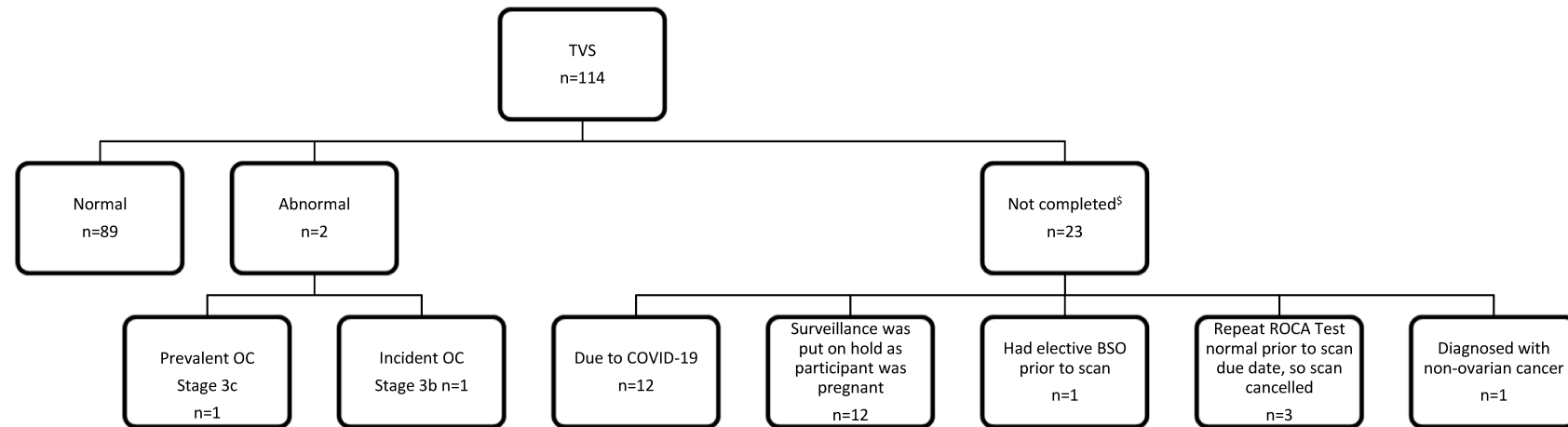
Key:
*Requested in 104 women
$ All repeat tests where indicated were normal
TVS = Trans Vaginal Ultrasound Scan
OC =Ovarian Cancer

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Supplementary Table 4: Reasons for not providing blood samples

Never returned a sample n=67	
Reason	**Number**
Reason not ascertained	40
Too busy to provide sample	9
Planning RRSO imminently	5
Difficulty getting an appointment for blood sample	4
Health issues	4
Moved away	2
Sample lost in transit	2
Did not receive blood packs	1
Returned 1 or more sample n=44	
Reason	**Number**
Reason not ascertained	24
Difficulty getting an appointment for blood sample	6
Too busy to provide sample	6
Health issues	3
Moved away	2
Did not receive blood packs	1
Pregnancy	1
Found result letters stressful	1

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Supplementary information on the cost-effectiveness analysis of the ALDO surveillance programme

Methods

This supplementary information outlines the model used to estimate the cost-effectiveness of the ALDO surveillance programme for women with a pathogenic BRCA variant, who are at high risk of developing ovarian cancer (OC) as based on the reported ALDO clinical results. We perform a simulated incremental cost-effectiveness analysis of the ALDO surveillance screening programme compared to a no-screening arm over the lifetime period of a modelled population cohort of 1,000 at risk women using a Markov cohort approach. The analysis is based on individual patient level data collected during the ALDO study for the surveillance arm, and collected from relevant literature for the control, no-surveillance arm. The cost-effectiveness perspective adopted in this study is the UK National Health Service (NHS). The NHS is the major provider of all cancer services within the UK. We consequently use the UK National Institute of Health and Care Excellence (NICE) recommended discount rate of 1.5% per annum for public health interventions[1].

We initiate the ROCA surveillance testing programme in woman of 35 years of age and adopt a Markov population cohort model to examine the incremental cost-effectiveness of the programme and compare it to a control arm where women are assumed to have the self-determined choice of undertaking risk-reducing salpingo-oophorectomy (RRSO) or that they may develop symptoms due to an OC and enter associated therapy. The Markov model uses a simulation of 1,000 women who face progression through a number of health states to death, either from OC or a competing risk (these are given in Figure S3). The model follows the individuals from the point they undergo gene testing for their BRCA status until death using annual cycles.

The effectiveness measures used are life years gained (LYG) and quality adjusted life years (QALY) gained. These are based on extrapolations of the detection of OC in the surveillance arm and the development of OC in the control arm, taking into account the choice to undergo RRSO in both arms. The extrapolations are made, in the normal Markov cohort manner, through allocating transition probabilities to the population to move them through various health states.

In any given year (model cycle) an individual can decline or defer RRSO or opt for RRSO. For individuals who do not opt for RRSO the model assumptions and the data sources used to populate

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the model are detailed below. Estimates of the annual risk of OC by age for BRCA-carriers are taken from Kotsopoulos et al (2018)[2] for both arms, and the breakdown into early (stages 1 and 2) and late (stages 3 and 4) cancer from the ALDO data for the surveillance arm and from Rosenthal et al (2017)[3] for the control arm.

The probabilities of the transition from healthy (i.e. no cancer) to death for both arms are based on BRCA-carrier specific death rates given in Mai (2009)[4] up to age 55 years after which the probabilities are assumed equal to the ONS mortality, again for both arms. The probability of transition from the state of advanced cancer to death for the first 12 years is based on Rubin et al (1996)[5] and these are then adjusted by the relative risk (hazard ratios) reported by Lavie et al (2019)[6] to give the probabilities of transition from the early cancer state to death. Beyond 12 years individuals are assigned the same probabilities of transition from both advanced and early cancer state to death as given by the ONS for the general UK population[7], given that after 12 years they are considered to be in complete remission. This assumption is based on expert opinion and supported by the lack of BRCA-carrier specific life tables and holds for both arms.

For individuals who opt for RRSO the model assumptions and the data sources used to populate the model follow. To determine the number of individuals who decide to undergo RRSO, age- and time from genetic test- dependent estimates of the proportion of individuals opting for RRSO are taken from Evans et al (2009)[8] and applied to both arms. Following RRSO an individual can be diagnosed free of OC, with early OC or with advanced OC. The estimates for the above prevalence figures at the time of RRSO were obtained from Kotsopoulos et al (2018)[2]. The corresponding probabilities from transition to death from any of the above health states were obtained from the same sources as for the individuals in the same health states who had not opted for RRSO described above. This approach was adopted for both arms.

We use quality of life (QoL) data taken from Edwards, Barton, Thurgar et al. (2015)[9] who reviewed 187 papers reporting QoL data relating to OC, of which 27 provided data suitable for use in economic evaluations. While their concern was with advanced recurrent and refractory OC, the study reported QoL tariffs for stable and progressive disease, estimated at 0.718 and 0.649 respectively. These values were based on a sample population of over 600 patients and were generally representative of values used for similar states in other studies. We take these values to proxy the QoL tariffs for early-stage OC (0.718) and advanced OC (0.649) within the Markov model.

We analyse only direct health service costs covering the surveillance and control populations and the subsequent treatment costs. Resource usage was based on the identification of surveillance visits, blood tests, clinic visits, surgery and follow-up clinical assessment. In addition, chemotherapy agents and the number of cycles were identified for those treated for OC as based on NICE Guidance Ovarian Cancer Overview 2019.[10]

For the early cancer state all women are assumed to receive surgery and chemotherapy of 6 cycles of paclitaxel and carboplatin. Following this, 80% (platinum-sensitive relapse) receive a further 6 cycles of paclitaxel and carboplatin and the remaining 20% (platinum-resistant relapse) receive a further 6 cycles of weekly paclitaxel. For the advanced cancer state all women are assumed to receive surgery and chemotherapy (6 cycles of carboplatin and paclitaxel) followed by maintenance therapy with Olaparib alone (80% of patients) or Olaparib and Bevazicumab (20% of patients). Following this, 80% (platinum-sensitive relapse) receive a further 6 cycles of paclitaxel and carboplatin and the remaining 20% (platinum-resistant relapse) receive a further 6 cycles of weekly paclitaxel and Best Supportive Care (BSC). No overall survival benefit from use of maintenance Olaparib was assumed.[11] The resulting overall annual per patient surgery and chemotherapy (including maintenance) cost is £48,309 for these individuals and £21,515 for the individuals in the early cancer state.

All surveillance and treatments were recorded within NHS settings. The 2019-2020 NHS tariff prices associated with relevant hospital episodes (in-patient, day case and out-patient), procedures, blood tests and clinics were attached to these visits (UK Dept. of Health, 2020).[12] The unit costs arising from treatment of OC with chemotherapy agents were gained from a number of secondary sources, primarily reports from NICE (UK)[13] and the British National Formulary (BNF) prices 2020,[14] as reported by NHS England, and for BSC at end of life.[15]

The unit cost of the CA125-ROCA test used to predict the likelihood of the presence of OC was based on the current price of £150.[16] Although the blood tests forming the basis of the ROCA were administered through GPs in the ALDO study, we make the conservative assumption that an out-patient visit is incurred in testing. This estimate was used in the base-case analysis and subjected to sensitivity analysis to account for the uncertainty surrounding the estimated value.

On the basis of the data and assumptions outlined above we find that the ROCA surveillance testing programme is cost saving to the NHS. The number of life years gained by the surveillance

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programme is 0.046 and the number of QALYs gained is 0.179. The control arm incurs a cost of £220,677 per patient over lifetime while the ROCA surveillance arm incurs a cost of £202,337 per patient over lifetime. As such the ROCA surveillance arm provides health benefit at lower cost and is deemed cost saving for the base-case analysis (the calculated ICER is estimated to be -£102,496 per QALY gained).

Various sensitivity analyses were undertaken. First, a threshold ROCA price was established through sensitivity analysis where the ALDO surveillance arm, given the baseline assumptions would no longer be considered cost saving. This threshold for the ROCA price is established at £585. If the ROCA algorithm were priced at £585, the incremental cost-effectiveness for the ALDO surveillance arm becomes £987 per QALY over a lifetime. This means the ALDO surveillance remains highly cost-effective, given current NHS England guidance, at this price.

In a separate sensitivity analysis we considered the impact on the ICER if the surveillance was stopped for women in older age groups, specifically, if the ALDO surveillance algorithm was not extended beyond ages 80, 75, 70, or 50. In all cases the ALDO surveillance remained cost saving. Further sensitivity analyses considered the impact on the ICER of different cancer detection rates. In the base-case analysis the detection of early stage cancers was set at 33.3% and that of advanced cancers at 66.7% as based on the ALDO programme results. In this set of sensitivity analyses, given the small numbers in ALDO, the detection rate of early cancers was increased by an absolute 10% and then decreased by an absolute 10% from the detection rate used in the base-case analysis. In both cases the ALDO surveillance remained cost saving. Finally, at a detection rate of 11.5% for early stage cancer, the ALDO surveillance programme reverted from being cost-saving to being cost-effective.

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Table A9: ALDO Collaborators, Project Steering Committee, Outcomes Committee members

Centre	Collaborators
St Bartholomew's Hospital, London, UK	Ranjit Manchanda
Birmingham Women's Hospital, UK	Jonathon Hoffman
Birmingham City Hospital, UK	Janos Balega
All Wales Medical Genomics Service, Swansea, UK	Alex Murray
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Clinical Genetics, Guy's and St Thomas' NHS Foundation Trust, London, UK	Louise Izatt, Anju Kulkarni and Vishakha Tripathi
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The Leeds Teaching Hospitals NHS Trust, Leeds, UK	Tim Broadhead
Clinical Genetics, Liverpool Women's NHS Foundation Trust, UK	Lynn Greenhalgh
Liverpool Women's NHS Foundation Trust, UK	Sian Taylor
Manchester Centre for Genomic Medicine, UK	Gareth Evans
Saint Mary's Hospital, Manchester	Richard Edmondson
North Tees and Hartlepool Foundation Trust, UK	Mary George
The North West Thames Regional Genetics Service, UK	Angela Brady
Oxford Centre for Genomic Medicine, UK	Joyce Solomons
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University Hospital Southampton NHS Foundation Trust, UK	Richard Hadwin
Familial Cancer Clinic Department of Gynaecology, University College London Hospitals NHS Foundation Trust, UK	Adam Rosenthal

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Project Steering Committee	Usha Menon, Gareth Evans, Richard Edmondson, Emma Woodward, Munaza Ahmed, Ranjit Manchanda, Nasa Turabi (chair), Adam Rosenthal, Sue Philpott, Caroline Presho (Patient representative), Athena Lamnisos (CEO, The Eve Appeal), Helga Laszlo (NCL Cancer Alliance), Julie Barnes (CEO, Abcodia Ltd.)
Outcomes Committee	Adam Rosenthal, Naveena Singh, Malcolm Scott