# Novel one-stop Multidisciplinary Follow-Up Clinic significantly improves cancer risk management in BRCA1/2 carriers

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**ABSTRACT**

**Purpose:** To measure the impact of a multidisciplinary one-stop follow-up clinic (MDOSC) on breast and ovarian surveillance, risk reducing surgery and enrolment in clinical trials in BRCA1/2 carriers.

**Patients and Methods:** All BRCA1/2 carriers in our region were invited and chose which specialists to see in our MDOSC offering best practice using clinical protocols based on national guidelines and published data. Uptake was evaluated over 24 months recording numbers of individuals undergoing breast and ovarian surveillance, risk reducing surgery, newly diagnosed cancers, their method of detection and participation in clinical trials.

**Results:** 172 (60%) of invited BRCA1/2 carriers chose to attend the MDOSC. Breast surveillance was initiated in 88% and screening frequency altered in 14% of women to comply with national guidelines. Risk reducing salpingo-oophorectomy was chosen by 47% of women and an additional 39% were considering it. The rate of failure to remove fallopian tubes fell from 15% to 3% of procedures ($p<0.01$) and peritoneal washings and serial sectioning of tubes and ovaries rose from 25% and 14% before, to 67% ($p<0.001$) and 63% ($p<0.001$) procedures respectively, after initiation of our MDOSC. 24% of women considered and 18% decided to undergo risk reducing mastectomy during the follow-up period. Participation in clinical trials increased significantly from 51 to 229 enrolments ($p<0.001$).

**Conclusions**: Our novel MDOSC designed to devise an individually tailored cancer risk management strategy had a high uptake amongst our BRCA1/2 carriers. Attendance resulted in improved breast and ovarian cancer risk management.

## BACKGROUND

About 5% of breast and ovarian cancers are caused by germline mutations in high risk cancer susceptibility genes such as BRCA1 and BRCA2 Slattery ([1]), Colditz et al ([2]). Individuals with a mutation in the BRCA1 or BRCA2 gene have an up to 80% lifetime risk of developing breast cancer and an up to 45% lifetime risk of developing ovarian cancer Easton et al ([3]). Males with a BRCA2 mutation have an up to 6% lifetime risk of breast cancer and an up to 14% lifetime risk of prostate cancer. Individuals and families with an inherited predisposition to breast and ovarian cancer due to a BRCA1/BRCA2 mutation face many challenges such as coming to terms with a highly increased breast and ovarian cancer risk, facing complex decisions regarding surveillance and risk reducing options, deciding how to communicate the possibility of inherited cancer risk to their offspring and keeping up with newest research developments.

## PATIENTS AND METHODS

A 24 month “New Services and Innovations in Healthcare” grant from Guy’s and St Thomas Charity was obtained to establish an MDOSC for BRCA1/2 carriers. The aims of the MDOSC are summarized in Table 1. The MDOSC was run once a month. BRCA1/2 carriers in our region of Southeast London, Kent and East Sussex received an invitation letter. All individuals attending the MDOSC were seen by a genetic health care professional but could choose which specialists (Breast Surgeon, Gynaecologist, Oncologist, Psychologist and Research Nurse) to see. Breast and ovarian surveillance

results and histology reports of any risk reducing procedures or cancers were obtained before each clinic to inform the discussion at the multidisciplinary meeting preceding the MDOSC where an individually tailored counseling and management strategy was devised for each patient. Patients were allocated personal consecutive 30-minute appointments with each clinician they chose to see and informed on how long to expect to attend the MDOSC depending on the number of health care professionals they decided to see. Careful scheduling of all appointments and coordination of the MDOSC on the day by the clinic coordinator enabled the MDOSC to run smoothly without delays.

Participating health care professionals covered the following topics: Genetic health care professionals covered genetic issues such as cascade testing, prenatal testing, pre-implantation genetic diagnosis as well as breast surveillance. Gynaecological health care professionals covered ovarian surveillance, risk reducing salpingo-oophorectomy (RRSO), contraception, hormonal replacement therapy (HRT), prenatal and pre-implantation genetic diagnosis. Breast surgeons covered risk reducing and reconstructive options and the oncologist covered the nature of prior or planned oncology treatments, treatment trials and chemoprevention. The research nurse discussed all trials that individuals were eligible for. The psychologist discussed any issues raised by individuals attending the MDOSC and counselled women contemplating risk reducing mastectomies.

The MDOSC infrastructure, assuring interaction of all the relevant medical specialties offered best practice based on the National Institute of Health and

Clinical Excellence (NICE) guidelines “The classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care”([4]).

The NICE guidelines on familial breast cancer state that BRCA1/2 carriers should undergo annual mammograms and breast magnetic resonance imaging (MRI) from ages 30 – 50 and after 50 years of age individualised arrangements should be devised due to a lack of trial data. We decided to advise our BRCA1/2 carriers to have 18 monthly mammograms if > 50 years of age.

Specific protocols were developed for women opting for risk reducing surgery based on these guidelines and on published data. Our protocol for risk reducing mastectomy ensured that all possible breast reconstruction options (immediate and delayed) were discussed and demonstration material and pictures were used with women who opted for an appointment with our breast surgeon with specialist/oncoplastic and breast reconstructive skills. The risk of breast cancer being diagnosed following bilateral risk-reducing mastectomy was discussed. Women were offered peer support with access to other women who had undergone the procedure. Pre-operative counselling by our psychologist about psychosocial and sexual consequences of bilateral risk-reducing mastectomy was undertaken during attendance at the MDOSC or recommended to be undertaken after the appointment for women opting for risk reducing mastectomies.

Women opting for the removal of their ovaries and fallopian tubes and their treating gynaecologists were provided with a protocol recommending RRSO with laparoscopic inspection of the abdomino-pelvic cavity, peritoneal washings and routine endometrial curettage for women on Tamoxifen. Serial slicing (2mm) of the fallopian tubes and ovaries was recommended for histopathological processing. Furthermore, prescription of hormonal replacement therapy for premenopausal women who had not had breast cancer was suggested until the age of 50.

Uptake and satisfaction with the new service (to be reported elsewhere) was evaluated during 24 months, including numbers of individuals undergoing breast and ovarian surveillance, adherence to the recommended surveillance, numbers of individuals opting for and outcome of risk reducing surgery surgery, participation in clinical trials, number and stage of newly diagnosed cancers and their method of detection. Individuals who attended the MDOSC were contacted by mail/telephone 12 and 24 months after attending the MDOSC and a follow-up appointment was offered. Information on breast/ovarian surveillance and risk reducing surgery was collected and reports and histology reports were obtained prior to the MDOSC. All available data until the end of September 2008 were included in this report.

**Statistical analysis**

The data for uptake of interventions before as against after the start of the MDOSC were analysed using Chi-squared tests (2 x 2 contingency) to examine differences. Pearson's chi-squared (with Yates' continuity correction

and 1 degree of freedom) and corresponding p-values, significance levels, and odds ratios with 95% confidence intervals were calculated.

## RESULTS

**Patient characteristics:** Two hundred and eighty eight individuals were invited to attend the MDOSC between February 2006 and February 2008. 172 (60%) chose to attend. Thirty five (12%) of individuals did not want to attend the MDOSC at that time but asked for an appointment in one year's time. Thirty five (12%) did not respond and 46 (15%) declined our invitation. The reasons given were as follows: They were too old to travel or not feeling well, the MDOSC was too far away from where they lived, they had already had all the risk reducing surgery presently available or they had nothing to discuss. Characteristics of patients attending the MDOSC are summarized in Table 2. The median time between receiving the genetic test result and attending the MDOSC was 32 months with a range of 1-147 months.

**Breast and ovarian surveillance:** Twenty five (15%) of the 164 women seen in the MDOSC had undergone risk reducing breast surgery prior to attending the clinic. Sixteen women were too young to be eligible for breast surveillance according to the NICE guidelines on familial breast cancer. Table 3 details the type and frequency of breast surveillance that the 123 women, eligible for breast surveillance under the national guidelines, received prior to attending the MDOSC. One hundred and twenty three women were eligible for mammograms. Seventy six of 123 women were between 30 and 50 years old

and therefore eligible for annual mammograms and breast MRI scans. Twenty three of 123 (19%) did not undergo mammograms before attending the MDOSC and 67/76 (88%) of women did not undergo breast MRI scans before attending the MDOSC. In 17/123 (14%) of women the frequency of breast surveillance was altered to comply with the NICE guidelines on surveillance for familial breast cancer after attending the MDOSC. Two mammographically detected breast cancers were observed between February 2006 and September 2008 but no interval breast cancers.

As there is no ovarian surveillance of proven efficacy, ovarian surveillance was only offered as part of the UK Familial Ovarian Cancer Screening Study =UKFOCSS ([5]) where women ≥ 35 years of age undergo yearly vaginal ultrasounds as well 4-monthly CA-125 serum measurements. Seventy nine of 164 (48%) of women were ineligible for the study (30 women were < 35 years of age, 9 women had been diagnosed with ovarian cancer and 40 women had undergone risk reducing surgery to remove their ovaries prior to attending the MDOSC). Of the remaining 85 women, 39 received either yearly abdominal or transvaginal ultrasound and/or yearly CA-125 serum measurements prior to attending the MDOSC. Twenty six of these 39 women chose to undergo ovarian surveillance in the future within the UKFOCSS study and a further 32 women joined the study after attending the MDOSC.

**Risk reducing surgery:** Eighty eight (54%) of 164 women had been diagnosed with breast cancer, 20 (12%) women had undergone a contra lateral and 5 (4%) women had undergone a bilateral risk reducing mastectomy

prior to attending the MDOSC. After attending the MDOSC, 33 (24%) seriously considered risk reducing mastectomy, 12 (9%) decided to have a risk reducing mastectomy and 13 (9%) of 139 women had undergone the procedure by September 2008 (see Table 3).

As outlined above, 79 women were ineligible for RRSO. For details of patient numbers undergoing surgery and histological findings see Table 4 and for details of types of operations and histo-pathological processing in the two groups of women see Table 5.

**Clinical trial enrolment**

Individuals attending the MDOSC were offered enrolment into the following trials: UKFOCCS([5]), Epidemiological Study of Familial Breast Cancer=EMBRACE([6]), Prevention and Observation of Surgical Endpoints=PROSE ([7]), Identification of Men with a Genetic Predisposition to Prostate Cancer: Targeted Screening in BRCA1/2 Mutation Carriers and Controls=IMPACT ([8]), International Breast Cancer Intervention Study=IBIS-2 ([9]) and the BRCA trial ([10]). For details of patients recruited to each trial see Figure 1. All 172 pts attending the MDOSC were eligible for the EMBRACE trial: 46 (27%) had already been recruited prior to attending the MDOSC. Of the remaining 126 patients, 2 declined an appointment with the research nurse, 23 did not send the questionnaire and consent form back handed to them during MDOSC attendance resulting in an enrolment of 101 (80%) of patients attending the MDOSC as shown in Table 5. Recruitment to

UKFOCCS also improved significantly from 5 patients before to 46 patients after attending the MDOSC ($p<0.001$) as shown in Table 5.

## DISCUSSION

Individuals who undergo genetic testing for BRCA1/2 mutations receive pre- and post-test counselling by genetic health care professionals as required by international guidelines[4], American Society of Clinical Oncology Policy Statement Update ([11]). Individuals with a pathogenic BRCA1/2 mutation usually discuss their cancer risk management with a genetic health care professional at one or several post-test counselling sessions and if they opt for risk reducing procedure, a referral is made to the respective specialist surgeon.

The most important decision for women with a BRCA1/2 mutation is whether to consider risk reducing surgery. Risk reducing mastectomy for example is very effective in reducing the risk of breast cancer by ≥ 90% Bernadette et al ([12]), while RRSO can reduce ovarian/fallopian tube cancer risk by 95% and breast cancer risk by up to 50% in premenopausal women Rebbeck et al ([13]), Kauuf et al ([14]). Other options include breast surveillance, chemoprevention and participation in ovarian cancer screening trials. However, risk reducing breast surgery is a highly complex procedure from medical, physical and psychological viewpoints and needs careful consideration and counselling and RRSO can result in significant symptoms in women unable to take HRT. Therefore, we reasoned that a one-stop clinic providing BRCA1/2 carriers with an opportunity to discuss all cancer management options and receive

psychological support and counselling at the same time, combined with a preceding multidisciplinary meeting of all health care professionals to devise an individualized cancer management strategy, would enable BRCA1/2 carriers to make fully informed and supported decisions on issues pertinent to their BRCA1/2 carrier status.

The majority of invited BRCA1/2 carriers chose to attend the MDOSC. The most popular risk reducing procedure was RRSO with a significant increase in uptake (see Table 5). After attending the MDOSC, 40 (47%) of 85 women ≥ 35 years with intact ovaries decided to undergo this procedure and 33 (39%) of 85 women were seriously considering it. These findings demonstrate that the majority of women choosing to attend the MDOSC want to reduce their ovarian/fallopian tube cancer risk. The decision to opt for surgery may also be influenced by the awareness that RRSO, if performed premenopausally, delivers additional benefits with regard to breast cancer risk reduction.

The MDOSC provided women with crucial information relevant to their chosen surgery and empowered them to discuss the appropriate approach with their surgeon. Our MDOSC devised protocols have also improved effective communication with other surgical teams as evidenced by an improvement in surgical protocol compliance. 6/40 (15%) women undergoing risk reducing ovarian surgery before attending the MDOSC did not have their fallopian tubes removed compared to only 1/28 (3%) women undergoing RRSO after attending the MDOSC. Furthermore, the number of women who had peritoneal washings and 2 mm slicing of their fallopian tubes and ovaries rose

from 9/36 (25%) and 5/36 (14%) respectively before attending the MDOSC to 18/27 (67%) and 17/27 (63%) respectively after attending the MDOSC. Our findings highlight the importance of providing surgeons performing a RRSO with a protocol tailored to the biology of BRCA1/2 associated ovarian/tubal malignancies as the lifetime risk of fallopian tube cancers Brose et al ([15]), Piek et al ([16]) in BRCA1/2 carriers is much higher than in the general population and as a recent study showed that the fimbrial end of the fallopian tube appears to be the dominant site of origin for early malignancies on BRCA1/2 carriers Callahan et al ([17]). Furthermore, as up to 2.5% of BRCA1/2 mutation carrying women undergoing an RRSO have an occult malignancy Powell et al ([18]), rigorous operative and pathological sampling is of crucial importance.

Sixteen percent of our BRCA1/2 carriers chose risk reducing breast surgery prior to attending and 42% either seriously considered (24%) or decided to undergo (18%) risk reducing mastectomy after attending the MDOSC. Although the uptake of risk reducing mastectomy in BRCA1/2 mutation carrying women varies widely among different countries Metcalfe et al ([19]), this percentage is within the percentages reported for the UK[20]. Interestingly, in contrast to RRSO, MDOSC attendance did not result in an increased uptake of risk reducing breast surgery (see Table 5).

Despite having undergone pre- and post-test genetic counselling, 19% and 88% of women eligible for breast surveillance under the national guidelines did not receive mammograms and breast MRI scans respectively before attending the MDOSC and a further 14% had their breast surveillance

schedules altered to adhere to national guidelines after attending the MDOSC. These findings underline the importance of a structured follow-up of individuals carrying a cancer predisposing gene mutation to ensure that surveillance recommendations are put into clinical practice. However, it should be noted that although annual MRI scans have been recommended for BRCA carriers since 2006 ([4], access to this surveillance currently depends on the availability of facilities and expertise, and funding agreement from the patient's Primary Care Trust. This situation will be rectified once the National Cancer Reform Strategy ([21]) is implemented across England and Wales.

As there are many unanswered research questions in inherited breast/ovarian cancer, BRCA1/2 carriers should be given the opportunity to participate in clinical trials. Like the multidisciplinary follow up BRCA1/2 carrier clinic currently offered at the Royal Marsden Hospital in London Bancroft et al ([22]), our MDOSC significantly increased enrolment into research trials.

In conclusion, attendance at our MDOSC resulted in a significant improvement of breast and ovarian cancer risk management in our BRCA1/2 carriers. Based on our results, Guy's and St Thomas Foundation Trust have decided to fund the MDOSC as a clinical service.

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**Figure Legend**

Figure 1: Number of patients enrolled in clinical trials before and after attending the MDOSC.

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