Screening for Gynaecological Cancer and Risk Reducing Surgery in Women at High Risk of Ovarian / Fallopian Tube or Endometrial Cancer - Full Clinical Guideline

Gynae/09:22/M5

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1. Introduction

Approximately 5% of endometrial cancer (EC) and 20% of epithelial ovarian cancer (OC) are hereditary [1-5]. Most genetic abnormalities predisposing to OC occur in germ line mutations in the BRCA1 and BRCA2 genes or mismatch repair genes in Lynch syndrome (LS) [6, 7]. The cumulative life time risk of OC is 40-50% in BRCA1 carriers, 20-30% in BRCA2 carriers and 10% in HNPCC carriers [8] compared to 2% in the general population [9], making these individuals at high risk of developing OC.

Women with a familial/genetic predisposition develop OC at a younger age. The risk of OC in women under 50 who carry the BRCA1 or BRCA 2 gene is 23-29% and 0.4-3.3% respectively [10, 11] compared to 0.5% for the same age group in the general population. Over 80% of the cases of OC in general population are diagnosed after the age of 50 [9].

OC tends to present with non-specific symptoms [8] which can delay diagnosis and hence most women present with advanced (stage 3-4) disease. Often treatment of advanced disease is not curative [12]. The survival of women with OC is directly related to the stage at presentation with 92% of women presenting with stage 1 disease surviving 5 years compared to 2% presenting with stage 3 disease [13].

The most common genetic abnormality predisposing to EC is Lynch syndrome caused by germ line mutations in the DNA mismatch repair (MMR) genes (MSH2, MLH1, MSH6, PMS2) [14-17]. This condition predisposes to early-onset cancer of colorectal, endometrial, ovarian, gastric, small bowel, hepatobiliary, brain, ureteric and renal pelvic origins [18]. The lifetime risk for EC is 40–60% compared with a risk of 3% in the general population. The risk of EC may be higher than

the risk of colorectal cancer especially in women with the MSH6 mutation [19]. For OC, the lifetime risk is 10–12% compared with the general population risk of 2% [20].

Lynch-related OCs are often early stage and moderately or well differentiated. Women with Lynch syndrome also have a greater likelihood of synchronous EC than other OC patients [21]. Population-based studies suggest that MMR gene mutations are found in 9% of EC cases under the age of 50 years [22].

2. Purpose and Outcomes

To detect OC or EC in the early stage resulting in a reduction in the mortality from the disease & to consider strategies to prevent cancers.

3. Abbreviations

NCCN	-	National Comprehensive Cancer Network
OC	-	Ovarian Cancer
RDH	-	Royal Derby Hospital
UKFOCSS	-	United Kingdom Familial Ovarian Cancer Screening Study
ROCA	-	Risk of Ovarian Cancer Algorithm
PPV	-	Positive Prediction value
NPV	-	Negative Prediction value
TVS	-	Transvaginal Ultrasound Scam
RRBSO	-	Risk reducing Bilateral Salpingo-oophorectomy
RR	-	Risk reducing
BGCS	-	British Gynaecological Cancer Society
CS	-	Cowden Syndrome
EC	-	Endometrial Cancer
RRS	-	Risk Reducing Surgery

4. Key Responsibilities and Duties

- To ensure high risk patients are referred and assessed appropriately in the family history clinic
- To discuss the limitation of screening and role of risk reducing (RR) surgery
- To ensure compliance with the guidelines

5. Criteria for defining individuals/families that are at high risk of developing gynecological cancer

>10% lifetime risk of developing OC or EC [23]

- Families with a BRCA1/2 carrier probability of 10% or more based on Manchester score (combined Manchester score >15) (See appendix A).
- The family contained two or more individuals with OC at any age who were first degree relatives*
- The family contained one individual with OC at any age and one individual with breast cancer diagnosed at <50 years of age who were first degree relatives*
- The family contained one individual with OC at any age and two individuals with breast cancer diagnosed at <60 years of age, who are connected by first degree relationship*
- The family contains one individual affected by both OC and breast cancer who is a first degree relative
- The family contained an affected individual with a mutation of one of the known OC or EC predisposing genes (BRCA1, BRCA2, MLH1, MSH1, MSH6, PMS1, PMS2, BRIP1, RAD51C or RAD51D) or genes that have been more controversially linked to an increased risk of OC or which are associated with rarer subtypes of OC or EC (PALB2, STK11, TP53, MSH2, EPCAM, PTEN)
- Three or more family members with colon cancer, or two with colon cancer and one with stomach, ovarian, endometrial, urinary tract or small bowel cancer in two generations. One of these cancers must be diagnosed under age 50 years

- Known carrier of relevant gene mutations (BRCA1, BRCA2, MLH1, MSH1, MSH6, PMS1, PMS2, BRIP1, RAD51C or RAD51D) or genes that have been more controversially linked to an increased risk of OC or which are associated with rarer subtypes of OC or EC (PALB2, STK11, TP53, MSH2, EPCAM, PTEN)
- Any patient affected by breast and ovarian cancer who have not received genetic testing via the mainstreaming pathway.

**In these categories a second degree relative may be counted if the transmission is via the paternal line (e.g. a sister and a paternal aunt or a sister and two paternal aunts).*

All women with early onset endometrial cancer (age of diagnosis <50 years) should have their tumor tested for Lynch mutations and this should be arranged following discussion at the gynaecology MDT.

Any women can be tested for genetic conditions in accordance with the National Genomic Test Directory.

6. Screening in women at a high risk of developing ovarian / fallopian tube or endometrial cancer (Including screening in low risk women)

Ovarian Cancer Screening

Key points

- All patients should be aware of the symptoms and signs of OC and be aware of the appropriate pathways to investigate any symptoms
- There is no evidence at present for population OC screening in low risk women (background risk equivalent to the general population).
- There is no evidence at present for population OC screening in women with a high risk of developing OC
- TVS and serum CA125 performed yearly may be used at the clinician's discretion in women who wish to delay RRBSO.

Low risk

Although this guideline is focused on the risk assessment of patients with a high risk of OC, patients may attend who have no elevated risk of OC compared to the general population. The following studies are included for completeness. The American Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial demonstrated that screening asymptomatic postmenopausal women with a single threshold value of CA125 does not result in reduction of mortality, despite 13 years of long term follow up. Diagnostic evaluation following a false-positive screening test result was associated with complications [24, 25].

The UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) trial randomized 202,000 women to observation alone, multimodal screening (MMS), with an algorithm based on serial values of CA125 and follow on TVS for abnormal results, or serial TVS alone. The results showed no reduction in mortality in the primary analysis, but a possible reduction in mortality after exclusion of prevalent cases after 7 years of follow-up. There was a suggestion that a survival benefit may be seen after a prolonged period of follow up and further analysis of this study is ongoing [26]. At present there is no evidence of survival benefit of screening in women with a background (low) risk of OC.

High risk

UKFOCSS phase 1 study [23] recruited and screened 3563 women who had more than 10% lifetime risk of developing OC with annual TVS and serum CA125. This study evaluated the screening performance characteristics, impact of delayed screening and surgical intervention in the form of RRBSO.

Sensitivity, positive predictive value (PPV) and negative predictive value (NPV) for detection of all incident ovarian/fallopian tube cancers at 1 year after last annual screen was 81.3% (95% CI, 54.3-96%), 25.5% (95% CI, 14.3 to 40.0) and 99.9% (95% CI, 99.8 to 100) respectively. However only 4 (30.8%) of the 13 incident screen detected cancers were stage 1 or 2. Thus routine

screening is not sensitive enough to detect early stage disease. Moreover 33 of the total 37 ovarian/fallopian tube cancers were found in women with known predisposing genetic mutations putting them at the highest risk. This trial failed to show a significant impact on mortality as a result of screening in these high-risk women. The high NPV of a normal screen in these high-risk women (99.9% probability that a woman will not be diagnosed with ovarian cancer in the next year), may help these women to delay the RRS until they have completed their family.

A phase 2 analysis of the UKFOCSS study expanded the patient cohort to 4348 patients and investigated them with 4 monthly CA125 levels and yearly TVS. The purpose of this trial was to assess deviations from a patients' baseline CA125 level (the risk of ovarian cancer algorithm (ROCA)). Again, the results suggest a trend towards detection of lower volume disease that is more likely to be operable, but an overall survival benefit was unable to be demonstrated. In this study, of the 19 cancers detected within one year of a screen, 6 were detected during RRBSO [27]. Similar results were seen in a combined American analysis with potentially earlier stage detection but yet again, most cancers were detected during RRBSO [28].

Despite suggestions of earlier detection with ROCA screening algorithms, no survival benefit has yet been identified and this is consistent with previous studies into the clinico-pathological features of screen detected OC in high risk women that concluded that there is low likelihood of detecting early stage high grade serous cancers with screening and thus there may be no impact on mortality [29].

Screening with CA125 and TVS is unproven in high risk women. Due to the high NPV there may be value of screening in women from the age of 30-35 who wish to temporarily delay RRBSO in order to complete childbearing with yearly TVS and 4 monthly CA125 but this should only be utilized in women who intended to undergo RRBSO in the future. In those women undergoing screening, any increase in serum CA125 levels from baseline should be taken seriously.

Endometrial Cancer Screening

Key points

- Patients at increased risk of EC should be aware of the symptoms, signs and referral pathways
- Routine screening with TVS and endometrial biopsy is not indicated in asymptomatic low risk women
- Screening in Lynch syndrome with yearly endometrial biopsy (via a route determined by the consultant coordinating care) and TVS is acceptable but does not replace the role of RRS.

Low risk
There is no evidence that screening asymptomatic women in the general population with TVS or endometrial sampling reduces the mortality from EC. There are no recognised acceptable endometrial thicknesses in asymptomatic patients and there is no data to suggest survival benefit from screening asymptomatic women. Endometrial biopsy can result in discomfort, bleeding, infection and rarely uterine perforation. In asymptomatic women, up to 25% of endometrial biopsies may yield insufficient tissue for diagnosis. No studies have evaluated the efficacy of TVS or endometrial biopsy in reducing mortality from EC in the context of mass screening [30].

High risk
The efficacy of endometrial surveillance in Lynch syndrome is still unproven. All patients should be advised regarding the symptoms and signs of endometrial cancer and should be appropriately investigated for any abnormal bleeding including inter-menstrual bleeding or irregular heavy periods. Both the British Gynaecological Cancer Society (BGCS) and the National Comprehensive Cancer Network in the USA (NCCN) accept that screening can be offered.

- BGCS: TVS and endometrial biopsy from the age of 35 years
- NCCN: Endometrial biopsy every 1 or 2 years after counselling about the risks, benefits and limitations of screening.

Although the BGCS included TVS in its screening regime, the NCCN suggest caution as interpretation of findings in premenopausal women can be difficult. Screening in women with Lynch syndrome should not replace the role of RRS.

7. Risk reducing surgery in women at a high risk of developing ovarian / fallopian tube or endometrial cancer

Key Points

- RRBSO reduces OC risk by 80-96%.
- Residual risk of peritoneal cancer 1-6%
- Offer RRBSO after completion of family from 35-40 years (BRCA1) and 40-45 years (BRCA 2)
- Bilateral salpingectomy should be offered when hysterectomy is performed for benign reasons
- Bilateral salpingectomy is not yet proven as preventative measure for patients with a high risk of OC but patients should be offered inclusion into trials such as PROTECTOR
- Associations between Uterine serous cancer and BRCA mutations are unclear and does not justify alone the addition of a hysterectomy at the time of risk reducing surgery. Any decision for hysterectomy should be tailored individually to each women.
- BRIP1, RAD51C, RAD51D or PALB2 should be offered RRBSO 45-50 unless earlier onset OC in family members.
- Hysterectomy could be considered in select patients, especially to facilitate oestrogen-only HRT post operatively
- Patients with Lynch syndrome should be offered RR hysterectomy and BSO at a time depending on family history, family status, gene type and co-morbidities
- All women undergoing RRBSO prior to undergoing a natural menopause must be aware that this will make them postmenopausal.
- Assessment using the Canrisk software may be helpful in providing a more individualized risk assessment (done by Genetics)

A: BRCA1 and BRCA2 mutation carriers

Due to the lack of effective screening and poor survival associated with OC, RRBSO is offered to high risk women to prevent ovarian/fallopian tube cancers [31-33]. The OC risk reduction is 80-96 % with 1-6% residual risk of developing primary peritoneal cancer [34, 35].

Beyond a reduction in OC risk there is evidence that RRBSO prolongs overall survival. Studies have found a 60–76% reduction in overall mortality in BRCA1 and BRCA2 mutation carriers who have undergone RRBSO compared with those who have not. In a large prospective cohort study [36], women at a high risk of developing ovarian/fallopian tube cancers who undergo RRBSO, compared to the ones that did not, had lower all-cause mortality (3% vs 10%; HR, 0.40 [95% CI, 0.26-0.61]) and ovarian cancer-specific mortality (0.4% vs 3%; HR, 0.21 [95% CI, 0.06-0.80]) [37].

It has previously been suggested that RRBSO in premenopausal BRCA1 and BRCA2 mutation carriers also reduces their risk of developing breast cancer [38, 39, 40] this has not been confirmed in recent studies and as such, at this point, RRBSO should not be performed in BRCA1 and BRCA 2 carriers purely to reduce the risk of breast cancer [41].

The option of RRBSO should be discussed with all BRCA1 and BRCA2 mutation carriers after conclusion of childbearing. A BRCA1 mutation carrier's chance of developing OC increases significantly during her 40s. There is no threshold at which point either RRBSO should not or must be performed. The decision to choose to undergo surgery and the age at which it is performed rests with the women who wishes to reduce her risk. However to give a general guidance we suggest that RRS is undertaken between ages of 35-40 years [42]. The risk for BRCA2 mutation carriers appears at an older age than BRCA1 mutation carriers and again although the time and decision to proceed RRS rests with the affected women we suggest as guidance that RRS can be delayed until 45 years of age [10]. Although these guidance ages are meant to give a general approach to all affected women, the timing of surgery should be influenced by the onset of cancer in the patients' family.

5-6% of the high-risk women undergoing RRS will have occult neoplasia detected either at the time of surgery or on final pathological examination. Age ≥40 and BRCA1 or BRCA2 mutation carrier status have been shown to be significant predictors of occult neoplasia [43, 44].

Although traditionally RRBSO is the mainstay of risk reduction in BRCA carriers an additional hysterectomy could be considered in order to facilitate oestrogen-only HRT afterwards for:

i) women with a personal history of progesterone receptor +ve breast cancer
ii) in women who have previously poorly tolerated progesterone therapy
iii) in women with no personal history of breast cancer who are not planning on having risk reducing breast surgery

In women with no such issues, hysterectomy could be considered when the risk of increased morbidity with a laparoscopic hysterectomy are outweighed by the potential benefits: psychological benefits, symptomatic benefits, reduced risks of subsequent uterine pathology. The literature is unclear regarding the risk of uterine serous cancers in women with BRCA mutations. However, a resent meta-analysis (56) identified uterine serous cancer in 15/7429 (0.2%) of women with BRCA1 and 3/3546 (0.08%) of women with a BRCA2 mutation. As such the decision of hysterectomy needs to evaluated on an individual patient basis and not determined purely on the presence of a BRCA mutation.

Salpingectomy

It is likely that BRCA associated serous cancers arise from the fallopian tube from a lesion called serous tubal intraepithelial carcinoma (STIC), and subsequently spread to the ovary and peritoneum via retrograde sheading of malignant cells and not via direct invasion through the fallopian tube. It has been postulated that removal of the fallopian tubes with conservation of the ovaries offers an alternative surgical approach in younger women to reduce their risk of OC whilst avoiding an iatrogenic menopause. At present this surgical option is of unproven benefit as the long-term effect on OC incidence and mortality in this patient group remains unknown [45]. Studies are ongoing to evaluate this further [46]. Women should be offered inclusion into prospective studies looking at salpingectomy and delayed oophorectomy such as PROTECTOR.

Opportunistic removal of the fallopian tubes at hysterectomy or sterilization has minimal additional surgical risk to the patient [47]. A large American study demonstrated an increase in the proportion of women wishing to have their fallopian tubes removed at surgery for benign conditions but additionally no difference in re-admission rates, post-operative complications or blood transfusion compared to those with conservation of their fallopian tubes [48]. At present salpingectomy alone is not validated as a safe method of reducing the risk of OC in high risk patients. In patients undergoing hysterectomy for benign conditions prophylactic salpingectomy should be offered.

B: BRIP1 / RAD51C / RAD51D / PALB2 mutation carriers.

Offer RRBSO from age 45 – 50. The specific risks of OC are poorly quantified in women with this mutation. The NCCN suggest consideration of RRBSO from 45-50 years or earlier depending on the age of OC in family members. PALB2 mutation carriers have an elevated but quality quantified ovarian cancer and pending the results of further studies can be offered RRS in line with BRCA2 mutations from age 40-45.

C: Lynch Syndrome.

There are four main genes which, when mutated, can cause Lynch syndrome. These genes are called MLH1, MSH2, MSH6 and PMS2. Additionally in EPCAM can cause Lynch syndrome. Cancer risks vary depending on Gene type as well as other factors such as Age, Family History, Previous Cancers etc.

Although hysterectomy has not been shown to reduce EC mortality it has been shown to reduce EC incidence and thus patients should be considered for hysterectomy and BSO.

One study of 315 women with Lynch syndrome found that no OC or EC occurred in women who underwent RRS, whereas 33% of women who did not have surgery developed EC and 5.5% developed OC [49].

The timing of surgery depends upon whether the patients' family is complete, family history, co-morbidities and Lynch gene type. In general Risk Reducing surgery will involve hysterectomy and BSO however in women with a PMS-2 mutation hysterectomy alone is sufficient.

Age related Gene risks by Type are:

	MLH-1		MSH-2 & EPCAM		MSH-6		PMS-2	
Age	Endometrial	Ovarian	Endometrial	Ovarian	Endometrial	Ovarian	Endometrial	Ovarian
30	0%	0%	0%	0%	0%	0%	<1%	Population
40	2%	2%	2%	2%	2%	2%	<1%	Population
50	15%	6%	18%	11%	13%	2%	2%	Population
60	27%	10%	38%	13%	28%	2%	3%	Population
70	35%	11%	47%	17%	41%	11%	6%	Population
80	37%	11%	49%	17%	41%	11%	12%	Population

Useful information can be found in the Royal Marsden Publication "A Beginners Guide to Lynch" https://patientinfolibrary.royalmarsden.nhs.uk/document/download/1148

Management of rare syndromes

A: Cowden syndrome (CS)

CS is a cancer predisposition syndrome characterized by macrocephaly, multiple hamartomas and an increased risk of breast, thyroid, colorectal, melanoma, renal cell carcinoma and endometrial cancers. CS is a genetic syndrome usually caused by mutations in a gene known as PTEN. The lifetime risk of EC in CS approaches 30% [50]. No evidence is at present available regarding the benefits of endometrial screening although some have suggested yearly endometrial biopsies. Until further data is available these patients should be offered hysterectomy after completion of family although the efficacy of this treatment is yet unproven.

B: Peutz-Jeghers syndrome

Is caused by germ line mutations in the STK11 gene. Peutz-Jeghers syndrome is an autosomal dominant gastrointestinal polyposis disorder which confers an increased risk of breast, gastrointestinal and gynaecological tumours.

Women with PJS are at risk of developing typically benign sex cord stromal tumors and Sertoli cell tumours (18-21% lifetime risk), adenoma malignum of the cervix (10% life time risk) and EC (9% life time risk). Annual screening with cervical smears and yearly TVS from age 18 – 20 years have been suggested although definitive evidence for screening is lacking [51].

C: Li-Fraumeni syndrome

Li-Fraumeni syndrome is caused by germ line TP53 mutations. Classically patients have early onset sarcomas, breast cancer, adrenocortical carcinoma and childhood tumours. Gynaecological malignancies are unusual in LFS, the most commonly diagnosed being epithelial ovarian carcinoma, for which there are no definitive screening recommendations.

8. Hormone replacement therapy and bone protection

Key points

- HRT should be considered in all women
- HRT needs to be tailored to individual patients
- If prescribed, HRT should be commenced prior to discharge from hospital with a plan for dose adjustment made with the patients GP
- If HRT is contraindicated or unwanted in women aged <45, a plan should be made to address bone strength and cardiovascular risk farctors.

RRBSO in premenopausal women results in premature menopause with associated menopausal symptoms in the short term and leading to increased cardiovascular [52] and osteoporosis [53] risks in the long term. HRT in these women will ameliorate these symptoms and protect against

the long term effects. Moreover, use of HRT does not alter the suggested breast cancer risk reduction offered by RRBSO [37]. There is no cardiovascular risk for healthy women taking HRT up to 59 years of age. Subgroup analysis from large trials showed starting HRT in younger postmenopausal women may have a beneficial effect on cardiovascular health but the effect of this 'timing hypothesis' needs further research with well-designed trials [54]. Therefore HRT should be offered to premenopausal women (with no personal history of breast cancer) undergoing RRBSO until the age of their natural menopause (50-51 years) [55].

At 51, consider gradual dose reduction over the next 12 months - e.g half dose for 6 months then quarter dose for 6 months, then stop. If patient develops unacceptable symptoms during this time, consider continuation of HRT with annual discussion of risks vs benefits with specialist menopause services.

An approach to HRT is suggested below.

Genetic mutations (BRCA 1 or 2, RAD51C, RAD51D, BRIP1):
If RRBSO only - continuous combined HRT until 51 with Mirena IUS and oestrogen replacement
If RR TLH BSO – oestrogen only until 51

Genetic mutations (Lynch)
If RR TLH BSO - oestrogen only until 51

Genetic mutations (Cowden, Peutz-Jeghers, Li-Fraumeni):
Discuss with specialist menopause services on case by case basis.

Breast cancer

- Women should be made aware of the risks of an iatrogenic menopause both in terms of the immediate symptoms of oestrogen deficiency (which may be severe) and the long term consequences of oestrogen deficiency on bone, cardiovascular and neurological health. [57]
- All women (especially those under the age of 45) should have bone health managed as described below and should cardiovascular risk factors addressed.
- HRT (systemic and vaginal) is relatively contraindicated in women with a previous history of breast cancer. In symptomatic women therefore, complementary therapies and non-hormonal medications should be used in the first instance.
- If symptoms are severe and refractory to non-hormonal medications, HRT could be considered following discussion with a menopause specialist and the oncologists.
- Offer early review by specialist menopause if desire for HRT would be a significant factor in whether to proceed with RRS.
- In women with a history of breast cancer, whilst HRT should be avoid in the first instance, some may benefit from a hysterectomy to refine subsequent HRT discussions and can be considered in selected cases to allow oestrogen only HRT in the future.
- If considering RRS in premenopausal women or postmenopausal women currently taking HRT, then pre-operative discussion with specialist menopause service is often helpful.

If in any doubt, consult specialist menopause service / relevant breast service prior to surgery.

Bone Protection

If HRT cannot be used in those aged <45 who require RRBSO thus resulting in early menopause there is a significant osteoporosis risk. We suggest:

- a pre-operative discussion to ensure the patient is aware of the risk to bone health.
- the patient can be given information about lifestyle measures for self-management of bone health from the Royal Osteoporosis Society including exercises videos and fact sheets to print out https://theros.org.uk/information-and-support/osteoporosis/living-with-osteoporosis/exercise-and-physical-activity-for-osteoporosis/
- the patient can calculate their dietary calcium intake using https://www.osteoporosis.foundation/educational-hub/topic/calcium-calculator (also available as an app) which can also be used as a resource to optimise calcium intake achieve 1000mg calcium per day
- check vitamin D levels aiming for >50nmol/L

- in pre-menopausal patients who are not to be offered HRT, a DXA scan before or within 3 months of RRBSO, would provide a useful baseline of the patient's bone density and to determine whether a bone agent as an alternative to HRT would be required. If the patient has a suboptimal calcium intake and/or vitamin D levels are insufficient/deficient, adequately replace these for 3 months **before** obtaining the DXA. This can be done with dietary adjustment or prescription with a calcium and vitamin D supplement such as Accrete D3 or Adcal D3 1 tablet *bd* which provides calcium 1000mg and vit D 800 units daily
- if required, seek further advice from the osteoporosis service if DXA shows osteopenia or osteoporosis (T/Z score less than -1) who can assist further such as assist with a fracture risk assessment to decide on the need for treatment or advise on a follow-up DXA scan

9. Recommendations for management of women at high risk of developing ovarian / fallopian tube or endometrial cancer at Royal Derby Hospital

New referrals to the Family History Service consist of referrals from GP's/ genetic counselors/other gynae consultants/breast team through referral letters to Mr Phillips and Familial Cancer Specialist

The Family History Clinic is held in the gynae outpatient department.

Referral paperwork can be addressed to Consultant Gynaecological Oncologist (Mr Phillips (APS)) or Familial Cancer Specialist, via the Familial Cancer Service.

New patients who have had not had their family tree evaluated at all should be referred to the Familial Cancer Service for initial evaluation of risk and possibility of genetic testing.

Subsequently reviewes occur in clinic APSSC if they are known to have a inherited predisposition or have been assessed by genetics as being sufficiently high risk to be considering RRS.

Only high-risk women as defined by the criteria above and who wish to proceed further with the conversation about RRS should then be seen in the Family History Clinic (clinic code = APSFH) potentially also considered for referral to the genetics team in Nottingham or Birmingham (via a standardised referral form) for consideration of genetic testing if not already done.

10. Monitoring Compliance and Effectiveness

Monitoring requirement	Compliance to guideline
Monitoring method	Retrospective case note review
Report prepared by	Named individual undertaking audit
Monitoring report sent to	Gynae Development Committee
Frequency of report	As per agreed Audit forward programme

11. This Guideline was compiled from the following sources

BGCS Uterine Cancer Guidelines: Recommendations for Practice 2017
https://bgcs.org.uk/BGCS%20Endometrial%20Guidelines%202017.pdf

British Gynaecological Cancer Society (BGCS) Epithelial Ovarian / Fallopian Tube / Primary Peritoneal Cancer Guidelines: Recommendations for Practice 2017
https://bgcs.org.uk/BGCS%20Guidelines%20Ovarian%20Guidelines%202017.pdf

RCOG Scientific Impact Paper No. 48 Management of Women with a Genetic Predisposition to Gynaecological Cancers Feb 2015
https://www.rcog.org.uk/globalassets/documents/guidelines/scientific-impact-papers/sip48.pdf

RCOG Scientific Impact Paper No. 44 The Distal Fallopian Tube as the Origin of Non-Uterine Pelvic High-Grade Serous Carcinomas Nov 2014
https://www.rcog.org.uk/globalassets/documents/guidelines/scientific-impact-papers/sip44hgscs.pdf

NCCN Genetic/Familial High Risk Assessment: Colorectal Oct 2017
https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf

NCCN Ovarian cancer Including Fallopian Tube and Primary Peritoneal Cancer Nov 2017
https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf

NCCN Genetic/Familial High Risk Assessment: Breast and Ovarian Oct 2017
https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf

NHS England National Genomic Test Directory
https://www.england.nhs.uk/publication/national-genomic-test-directories/

ESHRE Guideline on the management of premature ovarian insufficiency
https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Management-of-premature-ovarian-insufficiency.aspx

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Key
Relative = first degree or second degree relative only, except when calculating Manchester score*

Triple negative breast cancer = breast tumour negative for oestrogen receptor (ER)*, progesterone receptor (PR) and HER2 expression[$]

Ovarian cancer scoring:
A serous peritoneal primary tumour or fallopian tube cancers should be considered as if an ovarian cancer

* 1 intervening unaffected female is allowed when calculating the Manchester score

*Manchester Score	
Cancer, age at diagnosis	**Score**
♀Breast Cancer, <30	11
♀ Breast Cancer, 30-39	8
♀ Breast Cancer, 40-49	6
♀ Breast Cancer, 50-59	4
♀ Breast Cancer, >59	2
♂Breast Cancer, <60	13
♂ Breast Cancer, >59	10
Ovarian Cancer,<60 (not mucinous, germ cell or borderline) Or if high grade serous and not related to index case through more than one intervening female over 60	13 15
Ovarian Cancer, >59 (not mucinous, germ cell or borderline) Or if high grade serous and not related to index case through more than one intervening female over 60	10 12
Pancreatic Cancer	1
Prostate Cancer, <60	2
Prostate Cancer, >59	1
Breast cancer path adjustment in index case only	
Grade 3	+2
Grade 1	-2
ER +ve	-1
ER -ve	+1
Triple negative	+4
Lobular breast cancer	-2
HER2+	-6
Ductal carcinoma in situ	-2
Adopted no known status in blood relatives	+4

Pathology adjustments to Manchester Table adapted from Evans DG, Harkness EF, Plaskocinska I, et al Pathology update to the Manchester Scoring System based on testing in over 4000 families Journal of Medical Genetics 2017;54:674-681.

Pathology adjustment only needs to be made for the proband alone i.e. no pathology needs to be sought for other family members according to the genetic testing directory.
Example 1) a 44 yr old woman with breast cancer of grade 3 ER-ve would score 6+2+1 =9
Example 2) a 54 yr old woman with breast cancer of grade 2 ER +ve would score 4+0-1= 3
Example 3) a 30 yr old woman with breast cancer of grade 1 ER+ HER2+ would score 8-2-1-6=-1
Example 4) a 65 yr old woman with breast cancer of grade3 triple negative would score 2+4+2=8

***See accompanying FAQs for common queries.**

Table 3 Proportion with mutations using the combined *BRCA1/2* score

	BRCA1	*BRCA2*	Combined
40+	34 (63%)	12 (23%)	46/54 (85%)
35–39	10 (31%)	9 (28%)	19/32 (59%)
30–34	12 (27%)	13 (29%)	25/45 (56%)
25–29	20 (21%)	16 (17%)	36/95 (38%)
20–24	19 (13%)	20 (14%)	39/143 (27%)
15–19	9 (5%)	24 (12%)	33/199 (17%)
19	4	2	6/24 (25%)
18	4	6	10/67 (15%)
17	0	7	7/27 (26%)
16	1	7	8/63 (12.5%)
14	0 (0%)	3 (3.5%)	3/85 (3.5%)
12	2 (2.5%)	1 (1%)	3/80 (3.5%)
0–14	2 (0.5%)	6 (1.5%)	8/353 (2%)
Total	107/921 (11.5%)	99/921 (11%)	204/921 (22.5%)

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Development of Guideline:	Mr A Phillips – Consultant Gynaecological Oncologist			
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Key Contact:	Cindy Meijer			