



SCOTTISH EXECUTIVE

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# **Cancer Genetics Services in Scotland**

Guidance to support the  
Implementation of Genetics Services for  
Breast, Ovarian and Colorectal Cancer  
Predisposition

Full Reference Document

Scottish Cancer Group  
Cancer Genetics Sub-Group

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## BACKGROUND AND RATIONALE

1. It has long been recognised that inherited genes cause some very rare forms of cancer, such as retinoblastoma and neurofibromatosis. However, it has only more recently been recognised that rapid progress has been made in understanding the role that inherited genes play in determining a proportion of the more common cancers, including breast, colorectal and ovarian cancer. Although there is still uncertainty about the precise contribution of inherited predisposition genes to the incidence of these cancers, the available evidence suggests that breast, colorectal and ovarian cancer have a number of common genetic features:
  - A small proportion of these cancers (about 5%) are caused by inherited genes which, though comparatively rare, confer very high lifetime risks of developing cancer. In some cases these lifetime risks may be as high as 80%.
  - Cancers caused by these high penetrance genes are more likely to occur at an early age than sporadic cancers, and 15-20% of the cancers diagnosed in people under the age of 50 may be accounted for by these genetic mutations.
  - There is some evidence that cancers caused by these inherited predisposition genes develop more rapidly than sporadic cancers.
  - Carriers of known genetic mutations, which confer high lifetime risks of developing breast, colorectal or ovarian cancer is also at significantly increased risk of developing other forms of cancer.
  - A further 10-20% of breast, colorectal and ovarian cancers may be caused by other inherited predisposition genes which are less penetrant but which confer some increased risk (more than 3 times the general population risk). These 'medium risk' genes have not yet been identified.
  - Familial clustering of the more common cancers may also be influenced by environmental and lifestyle factors as well as by chance.
2. Following a report by the Genetics Sub-Committee of the Priority Areas Cancer Team, the then Management Executive of the SOHHD provided funding for 5.5 Genetic nurse/associates. These individuals were to be employed to provide assistance to the Regional Genetics Units in their provision of a service to patients referred with a family history of cancer and for the evaluation of this service.
3. The following guidelines which have been produced are aimed at providing a service, which can be implemented and evaluated with the current provision of staff.

## **IMPLEMENTATION STRATEGIES**

An evidence base through which to plan and design protocols for the effective implementation of new health care interventions, is currently being developed through the Health Services Research Unit at the University of Aberdeen.

As each, individual non-genetic health care professional is unlikely to see on average more than 2 or 3 patients per annum with concerns relating to a family history of cancer, the implementation strategy for these new guidelines (outwith the Regional Genetics Unit) needs to be developed accordingly.

Simple strategies such as paper guidelines and didactic teaching are, by themselves unlikely to be effective. Evidence suggests that feedback from audit, local consensus processes and educational outreach by trained professionals are likely to be more effective in both the short and long term. It is planned to utilise a multifaceted approach to the education of both primary and secondary health care practitioners utilising:

- Specialty specific guidance in the form of paper guidelines eg CD-ROM for GPs, Appendices 7 and 8.
- Local and national meetings with consultants and GPs
- Feedback to the referring population of the interim and longer term results of audit of process and clinical outcomes
- Local interactions with the genetic Nurse/Associates re-enforcing referral guidelines and downstream process based on developing evidence.

### **I Primary Care**

- (i) Professional contact - organised and opportunistic
- (ii) By response letter - common across Scotland to all Referrals from primary and secondary care.

### **II Secondary and Tertiary Care**

- (i) Response letter as in I(ii)
- (ii) Screening - Professional meetings - Breast screening; surgeons- breast, general and colorectal surgeons; gynaecologists
- (iii) Contact with local colleagues

### **Roles and Responsibilities**

- (i) Referrals - primary and secondary
- (ii) Risk estimation, counseling and screening recommendations - Regional Genetics Units
- (iii) Screening co-ordination and facilitation - tertiary care. RGU not equipped with staff or technically to co-ordinate follow-up programme
- (iv) Communication and Information pathways
- (v) Individual and family communications
- (vi) Audit - Steering Committee; Clinical Standards Board (Audit by RGU, Screening Units more difficult)

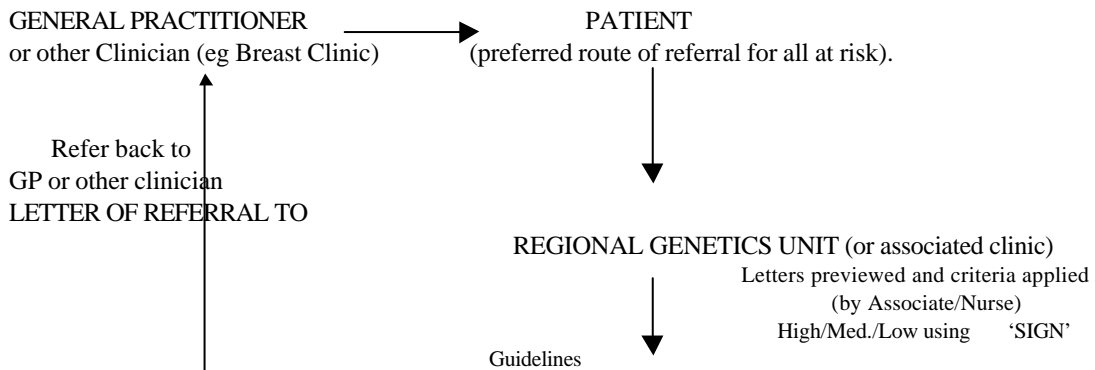
- (vii) Managed Clinical Networks - Letter to lead clinician; each RGU should contribute to appropriate MCN through attendance at Management meetings
- (viii) Clinical Standards Board - are we suitable for assessment and accreditation? Assess what - route of referral, risk estimation, screening availability, not attending for recommended screening, appropriate of surgical advice and of surgery, outcome measures
- (ix) Clinician in each area will take overall charge and must ensure link with Lead cancer Clinician

## **RESEARCH**

All research proposals of or based on data collected from the Service should be first submitted to the co-ordinating committee to ensure it will provide evidence and result in no interference with the service.

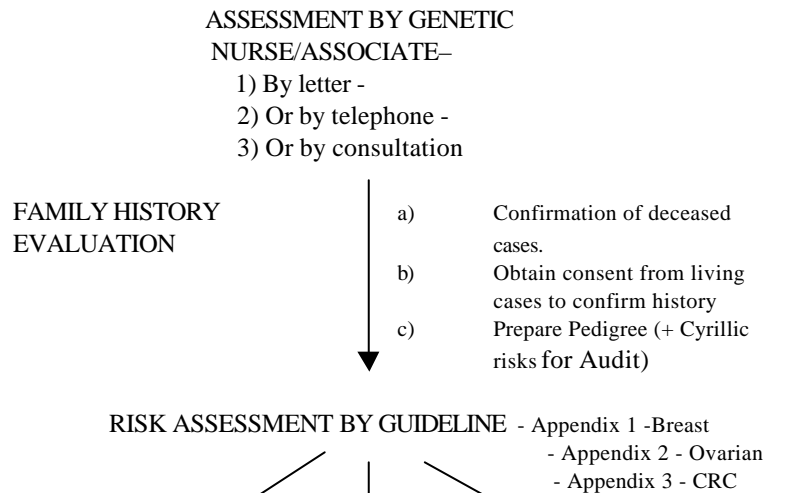
# FLOW CHART FOR PATIENT MANAGEMENT

## Step 1 – Referral Process



## Step 2

Confirmation of family history



## Step 3

Risk Stratification

LOW RISK GROUP      MEDIUM RISK GROUP      HIGH RISK GROUP – Appendix 4

Letter of reassurance to patient and GP (or other referring clinician)

(Confirming family history may move into different risk group. May also include complicated family history).

## Step 4

Counselling

Counselled by Genetic Counsellor

Counselling by Clinical Genetic Physician

With aid of support information sheets (Appendix 5 and 6)

## Step 5

Management

Screening

Gene Testing

Management

## **FLOW CHART FOR PATIENT MANAGEMENT**

### **STEP 1: Referral Process:**

Referrals of individuals with family and personal histories of cancer may come from General Practitioners or other clinicians. Most referrals will come direct to the Regional Genetics Unit, and unless local arrangements include other clinics, is the preferred route in order to prevent inappropriate referral to clinics such as the symptomatic breast clinics. Where possible, the Genetic Associate/Nurse should preview the referral letters and apply the Guidelines for referral. Referrals falling outside the current guidelines but possibly suggestive of a high risk situation should be discussed with the Consultant in Charge.

### **STEP 2: Confirmation of Family and Personal History**

Genetic Associate/Nurse should contact all patients prior to their first appointment to obtain a full family history with details of cases of cancer in the family. Where possible deceased cases should be confirmed using an appropriate source such as the Cancer Registers in the UK. Consent should be sought for living affected to confirm and specify diagnoses and a full pedigree produced with risk calculated by CYRILLIC 3 for audit purposes.

### **STEPS 3 and 4: Risk Stratification and Counselling**

*Each family must be encouraged to recontact RGU if Family History changes following initial counselling.*

#### **Determining Risk**

Genetic counsellors will base risk estimation and stratification on referral criteria (Tables 1, 2 and 3) producing:

- low risk (not fulfilling a category within the Guidelines) and
- medium or high risk (fulfilling criteria).

Clearly as family history evolves or is confirmed or refuted, individuals may move from apparent high risk to medium or low and vice versa.

*For audit (Cyrillic pedigrees and Cyrillic3 risk will be produced for all referrals involving breast cancer. This will be used for audit of variance between risks given from guidelines and risk from Cyrillic database).*

## **STEPS 3 and 4: Risk Stratification and Counselling**

### **BREAST**

#### **Low Risk Women:**

Low Risk – referrals whose family history is less significant than Referral Guidelines (Appendix 1).

Based on the referral criteria individuals deemed to be at low risk will be informed either:

- following telephone consultation by the Genetic Associate/Nurse followed by letter with a copy to GP,
- or**
- face to face consultation (with the Genetic Associate/Nurse) and then by letter to the patient and the GP.

*For Audit: A study of the satisfaction of women to these two different approaches should be carried out by questionnaire and information of repeat referrals from the General Practitioner back to the Regional Genetics Unit will be collected.*

Individuals deemed to be at low risk may be offered a single appointment for breast examination by a breast surgeon in certain centres, and again the effect of the intervention on satisfaction will be assessed as above.

#### **Medium and High Risk Individuals:**

Where the family history, once confirmed, falls within the guidelines for referral individuals will be classified as being at medium (Table 1) to high risk. *(Cyrillic calculation of risk will be carried out for audit).*

#### **Medium Risk Women:**

Women deemed to be at medium risk, based on referral guidelines, will be counselled by the genetic counsellor who will discuss with them information as recorded on the attached sheets (Appendix 5). Medium risk as defined in SIGN guidelines and as in Table 1.

- one 1<sup>st</sup> degree relative with bilateral breast
- one 1<sup>st</sup> degree relative with BrCa <40 yrs or male at any age;
- two 1<sup>st</sup> or 1<sup>st</sup> and 2<sup>nd</sup> degree relative with BrCa diagnosed under 60yrs or OvCa at any age on the same side of the family
- three 1<sup>st</sup> or 2<sup>nd</sup> degree relative with BrCa or OvCa on same side of family (at least one 1<sup>st</sup> degree relative unless history via father)

## **High Risk Women:**

High risk women may be in a family where the family history may include the following which predicts a likelihood of greater than 60% that a predisposing gene exists in the family. Such women will be counselled by a clinical genetic physician. This includes:

- gene carriers (eg. BRCA1, BRCA2, p53, pTEN)
- untested 1<sup>o</sup> relatives of gene carriers
- or one first degree relative(or 2<sup>o</sup> via intervening male relative) in a family with 4 or more relatives affected with breast cancer (bilateral breast cancer being counted as 2) breast cancer or ovarian or male breast cancer in three generations
- or one first degree relative(or 2<sup>o</sup> via intervening male relative) with breast and ovarian cancer.

## **STEPS 3 and 4: Risk Stratification and Counselling**

### **OVARIAN CANCER**

Risk estimation as referral guidelines (Table 3, Appendix 2).

**Low risk** – As for breast cancer.

Individuals with a single first degree relative, or a second degree relative by their father who have presented at any age are not appropriate for screening based on current risk estimations and screening options.

**Medium and high risk** – Table 3 and counselling as for breast cancer.

Medium risk largely as defined for the UKCCCR trial:

- two or more 1<sup>st</sup> or 1<sup>st</sup> and 2<sup>nd</sup> degree relatives with OvCa
- two 1<sup>st</sup> or 1<sup>st</sup> and 2<sup>nd</sup> degree relatives with OvCa at any age or BrCa diag under 50yrs;
- One OvCa and two breast cancers diagnosed less than 60 yrs on same side of family in 1<sup>st</sup> degree relatives or 2<sup>nd</sup> degree via a male
- two 1<sup>st</sup> or 2<sup>nd</sup> degree relative with CRC and an endometrial Ca and one with OvCa;
- one affected relative with OvCa and HNPCC family history;

*At least one case of ovarian cancer in each category*

High risk:

- an individual in family with BRCA1, BRCA2, hMLH1, hMSH2 or other predisposing gene;
- untested 1<sup>o</sup> relatives of gene carriers;

- 1° relative with breast and ovarian cancer
- At least one case of ovarian cancer in each category*

### **STEPS 3 and 4: Risk Stratification and Counselling**

#### **COLON**

See Table 2, Appendix 3

**Low risk** : counselling as for breast cancer.

**Medium risk** : counselling as for breast cancer.

A family should contain :

- 1 relative affected by colorectal cancer when aged <45yrs;
- 2 (one affected at less than 55 yrs) one a first degree relative of consult and or 3 affected with colorectal or endometrial cancer who are first degree relatives of each other) and one a first degree relative of consultand
- or two affected first degree relatives (one affected at less than 55 yrs)

#### **High risk** :

Where the family history shows a likelihood that a predisposing gene exists in the family, women will be counselled by a Clinical Geneticist. This includes:

- Gene carriers of HNPCC mutation
- Untested I° relatives of gene carriers
- People with a family history compatible with HNPCC

(i.e. Amsterdam criteria:  $\geq 3$  family members affected by CRC or  $\geq 2$  with CRC and one with endometrial cancer in  $\geq 2$  generations; one affected relative must be aged  $\leq 50$  at diagnosis, one of the relatives must be a I° of the other two.)

## **Step 5 : Management of 'At Risk' Individuals**

### **LOW RISK**

- Reassure/Healthy Life Style
- If breast cancer FH, letter and leaflet on Breast Awareness for female patients.
- Return to GP's care

### **MEDIUM RISK**

- Counselling
- Screening

### **Breast**

- Mammogram (and U/S as appropriate)– optimally at Breast Screening Center yearly.
- Physical Examination by Breast Clinician yearly.

Optimally all breast screening should be offered in an appropriately quality controlled environment with highly trained radiographers and radiologists. This situation clearly describes that available within the National Breast Screening Unit for women over 50 years of age.

Screening recommendations will be for breast screening from 35 to 40 years of age 2 yearly and from 40 to 50 years 1 yearly, or from 5 years younger than the youngest woman affected in the family (but not younger than 35 years or older than 40 years which ever is the youngest) until they reach 50 years of age and enter the National Screening Programme and 3 yearly to 64 years. Screening should be by mammography as above, one yearly physical examination of the breasts by a breast clinician, and discussion and advice on where to obtain information on breast awareness. (See "Education")

**Ovary** - from 35 years of age or 5 years younger than the youngest affected in the family which ever is the youngest until 65 years.

Appointment with a Gynaecological Clinician

Vaginal U/S – yearly

Ca 125 – yearly

Discussion of prophylactic oophorectomy

UKCCCR Trial

Screening should appropriately be co-ordinated by a clinician with a special interest in ovarian cancer. This should include ultrasound and Ca 125 estimation on one yearly basis. Women with a family history of both breast and ovarian cancer, women with a family history of ovarian cancer alone and women with a family consistent with HNPCC with ovarian cancer in the family should be entered into the UKCCCR trial. The limitations of ovarian screening should be explained to the woman.

## Colon

- Single colonoscopy at 35 years or aged >30 years if concerned.
- If clear, repeat colonoscopy at 55 years.
- Incomplete colonoscopy should be followed by a barium enema, preferably at the same hospital attendance.

Absolute risks are not in favour of biannual colonoscopy (see Appendix 8). The chance of biannual colonoscopy preventing cancer death is less than the risk of serious complication for people of all but the oldest age groups. Biannual colonoscopy is recommended in several screening policies and is current practice of some clinicians, but would generate very large numbers of procedures. However, the absolute 10-year cancer risk for a person aged 50 with 2 affected first degree relatives is 1.15%, whereas the population risk at age 70yrs is 3%. Thus, colonoscopic screening of the elderly could be more effective than screening people fulfilling “high risk” family history criteria. These guidelines accord with a recent consensus paper of US expert opinion.

**HIGH RISK** - Counselling  
- Screening

## Breast

- Mammogram (with U/S as appropriate) – optimally at Breast Screening Center yearly.
- Physical Examination by Breast Clinician yearly.

Breast screening in such women should be annually from 25 years of age for proven gene carriers (or from 5 years younger than the youngest affected in the family but no younger than 25 yrs, or older than 35yrs for other groups), continued yearly up until the age of 50, and eighteen monthly from 50 to 64 within the National Screening Programme and 3 yearly thereafter.

**Ovary** - from 35 years (or 5 yrs younger than the youngest case in the family) to 65 years.

- Appointment with appropriate clinician
- Vaginal U/S – yearly
- Ca 125 – yearly
- Discussion of prophylactic oophorectomy
- UKCCCR Trial

Prophylactic surgery (oophorectomy) should be discussed with high risk individuals (including those with BRCA1 and BRCA2 gene mutation, those with two first degree relatives affected with ovarian cancer and those with a first degree relative affected with breast cancer and three other female relatives on the same side affected with breast or ovarian cancer). Again, the limitations of ovarian screening should be discussed with the women. Women with a family history of both breast and ovarian cancer, women with a family history of ovarian cancer alone and women with a family consistent with HNPCC with ovarian cancer

in the family should be entered into the UKCCCR trial. Depending of the family history it may be appropriate to offer screening of other organs.

## **Colon**

- Colonoscopy every 2 years - from 30 yrs of age or from 5 yrs younger than the youngest case until aged 70yrs and possibility of a final scope at 75 years.
- Discuss prophylactic surgery - especially if recurrent polyps. Colectomy with ileorectal anastomosis are best option.
- Patients undergoing surgery for established colorectal cancer, require more extensive resection to reduce risk of metachronous tumour. Colonic tumour are best treated by colectomy and ileorectal anastomosis; rectal cancer usually would include an extensive left hemi-colectomy with anterior resection.

## **Endometrium and ovary -**

- Discuss annual gynaecological screening  
There is no established method for endometrial cancer screening and no available data on efficacy. Some centers offer clinical examination, transvaginal ultrasound and pipelle endometrial biopsy. Although in familial ovarian cancer, there is limited evidence for the efficacy of screening for ovarian cancer such screening does require evaluation.
- Discuss prophylactic hysterectomy and bilateral oophorectomy  
There is no clear evidence for benefit, but surgery may be preferable to pelvic screening for women past reproductive age, particularly if there is a history of gynecological cancer in the family.

## **Gastric -**

- Offer 2 yrly upper GI endoscopy, contemporaneous with colonoscopy from 50 years of age or 5 yrs younger than the first case in family. No available data on benefit, so a good case to recommend no screening outside trials.

## **Others-**

- consideration needs to be given to other screening for other cancers which may occur in specific families and are part of the HNPCC spectrum

## **Step 5: MANAGEMENT**

**Gene Testing :** Optimally gene testing should be available to all high risk families and predictive testing for at risk individuals within these families. Currently the identification of mutations in BRCA1, BRCA2, p53 and mismatch repair genes is only available in research studies.  
*Discussion with patients of future gene testing.*

### **Surgical Management Options for high risk individuals**

Managed clinical networks will include individuals with expertise in the surgical management of cancer in high risk individuals.

<b>Breast :</b>	Unaffected	No surgery but continued screening as above. Prophylactic surgery
	Affected	Lumpectomy ± adjuvant therapy Mastectomy ± preservation of nipple and areola complex ± adjuvant therapy Contralateral Prophylactic Mastectomy Reconstructive Surgery Prophylactic removal of ovaries

Presentation of unilateral cancer in a high-risk individual – advice should be given to both the patient and the surgeon on management of contra-lateral breast as well as the potential for recurrence in the ipsilateral breast.

<b>Ovary :</b>	Unaffected	No surgery but continued screening Prophylactic surgery.
	Affected	Protocols as for sporadic ovarian cancer
<b>CRC :</b>	Unaffected	No surgery but continued screening Prophylactic Surgery - Colectomy - no data available for effectiveness.

- Total hysterectomy for females.

: Affecteds: -Resection of tumour and a major portion of the bowel to decrease the risk of other tumour occurrence  $\pm$  adjuvant therapy, regular surveillance of any remaining large bowel  
-Prophylactic colectomy  
-Females – total hysterectomy and salpingo oophorectomy

## **Other Cancers**

When the patient presents with a cancer in the presence of a family history consistent with an increased risk of other cancers, management should include discussion with the patient, and other appropriate clinicians regarding other preventative measures for other cancers.

## **Psychological Support:**

The following should be offered an appointment with a clinical psychologist or other appropriately trained individual:

- Anyone undergoing predictive testing for mutations in cancer predisposing genes known to exist in their families,
- Anyone considering prophylactic surgery.
- Any individual with signs or symptoms of clinically significant psychological disturbance

## **Trials**

All patients should be invited to participate in current ongoing studies which include:

- MRI Breast Screening Trial (MARIBS)
- International Breast Cancer Intervention Study - Tamoxifen (IBIS)
- Epidemiology of BRCA1 & 2 Mutation Carriers (EMBRACE)
- National Familial Ovarian Cancer Screening Study (UKCCCR)
- Colorectal Cancer Genetic Susceptibility Study (COGS)
- Concerted Action for Polyp Prevention (CAPP2)
- IBIS and successor trials

## **Education**

Guidelines for referral and screening risks, as well as for screening protocol, should be made available to general surgeons, oncologists, gastroenterologists, radiologist and gynecological oncologists in all the Trusts within Scotland.

Information for clinicians on referral criteria, and on the recommendations for risk cut-offs for screening, and screening protocol should be provided by appropriate routes including the Scottish Cancer Groups and others as appropriate.

A planned programme of ongoing education is necessary for medical students and all qualified medical staff and relevant paramedical staff.

Implementation may play a part in the education process and will be facilitated following advice from the Scottish Cancer Group.

## **Quality Assurance**

The above broad guidelines for referral, risk estimation, screening and audit should be regarded as the appropriate process for cancer genetic referrals in Scotland. Quality assurance of this process may be assessed by yearly evaluation of random case records from each counsellor and clinician in each centre. This data should be provided in an anonymous form to the co-ordinating committee yearly.

## **Audits**

Audits should be carried out within the Regional Genetics Units as described in the Appendix and should include the downstream management facilities within Scotland. In addition to local audit of process in the Regional Genetics Units, audit of screening and outcome should be performed.

Clinical Standards Board of Scotland may audit some key items.

## **Cancer Registration**

Confirmation of cancer history can be obtained from the Cancer registries. For Scotland this information can be requested using the form appended in Appendix 12. For living individuals, a consent form signed by that individual must be included.

Yearly ascertainment of cancers occurring in consultands will be possible by supplying ISD with information in the consultands from the previous years in a cumulative file (ie each year give all of the previous years consultands since the initiation of the prospective study).

Information to be provided on consultands includes: **Name, DOB, NHS No., CHI number, Postcode.** This information can be provided on disc or Zip file in Access or Plain text file.

Databases for collecting Genetic Clinic data will need to undergo regular quality assurance. ISD may inform this process with SMR Data standards. eg QA sample of data annually. It will be necessary to ensure that all of the data collected is backed up in an appropriate manner and that the back up is safely stored in a fire and theft proofed manner. Sequential back up is recommended so that data from 1 week or 1 month previously can be used if any corruption enters the system.

Future plans need to be made for the central archiving of all data.

Tables 1, 2 and 3 summarizing the Referral and Screening Guidelines for Breast, Colorectal and Ovarian Cancer

**Table 1: Summary of Referral and Screening Guidelines for Breast Cancer**

<i>Risk Level</i>	<i>Criteria for Referral and Screening (Grade of Recommendation )</i>	<i>Screening (Grade of Recommendation)</i>	<i>Age to begin</i>	<i>end</i>
Low Risk	<ul style="list-style-type: none"> <li>anyone not fulfilling medium or high risk criteria</li> </ul> <p><b>( B - Evidence level III)</b></p>	<ul style="list-style-type: none"> <li>Reassure/Healthy Life Style</li> <li>If breast cancer FH, letter and leaflet on Breast Awareness for female patients.</li> <li>Return to GP's care</li> </ul> <p><b>( B - Evidence level III)</b></p>	50 (in BSP)	64
Medium Risk	<ul style="list-style-type: none"> <li>one 1<sup>st</sup> degree relative with bilateral breast</li> <li>one 1<sup>st</sup> degree relative with BrCa &lt;40 yrs or male at any age;</li> <li>two 1<sup>st</sup> or 1<sup>st</sup> and 2<sup>nd</sup> degree relative with BrCa diagnosed under 60yrs or OvCa at any age on the same side of the family</li> <li>three 1<sup>st</sup> or 2<sup>nd</sup> degree relative with BrCa or OvCa on same side of family (at least one 1<sup>st</sup> degree relative unless history via father)</li> </ul> <p><b>( C - Evidence level IV)</b></p>	<ul style="list-style-type: none"> <li>Mammogram ( 2 view) – optimally at Breast Screening Center</li> <li>Physical Examination by Breast Clinician yearly</li> </ul> <p><i>Screening from 5 yrs younger than the youngest case but not younger than 35 yrs or older than 40 yrs as indicated</i></p> <p><b>( C - Evidence level IV)</b></p>	35 (2 yrly) 40 (1 yrly) 50 (3yrly in BSP)  35 (1yrly)	40 50 64  64
High Risk	<ul style="list-style-type: none"> <li>an individual with BRCA1, BRCA2 or other predisposing gene;</li> <li>untested 1<sup>o</sup> relatives of gene carriers;</li> <li>first degree relatives of an affected (or 2<sup>o</sup> via intervening male relative) in a family with four or more relatives affected with either breast or ovarian cancer or male breast cancer in three generations</li> <li>or one first degree relative (or 2<sup>o</sup> via intervening male relative) with breast and ovarian cancer</li> </ul> <p><b>( B - Evidence level III)</b></p>	<ul style="list-style-type: none"> <li>Mammogram ( 2 view) – optimally at Breast Screening Center</li> <li>Physical Examination by Breast Clinician</li> <li>Ovarian screening as below</li> </ul> <p><i>Screening from 5 years younger than the youngest case not younger than 25yrs or older than 35yrs</i></p> <p><b>( B - Evidence level III)</b></p>	25 or +yrs (2yrly) 40 (1yrly) 50 (18mthly in BSP) Over 65 (3 yrly)  25 or + (1 yrly)	40 50 64  64

**Table 2: Summary of Referral and Screening Guidelines for Colorectal Cancer**

<b>Risk Level</b>	<b>Criteria for Referral and Screening (Grade of recommendation)</b>	<b>Screening (Grade of recommendation)</b>	<b>Age to begin</b>	<b>to end</b>
Low Risk	<ul style="list-style-type: none"> <li>anyone not fulfilling medium or high risk criteria</li> </ul> <p>( C - Evidence level IV)</p>	<ul style="list-style-type: none"> <li>Reassure/Healthy Life Style</li> <li>Return to GP's care</li> </ul> <p>( C - Evidence level IV)</p>		
Medium Risk	<ul style="list-style-type: none"> <li>1 first degree relative affected by colorectal cancer when aged &lt;45yrs;</li> <li>2 (one CRC less than 55 yrs) or 3 affecteds with colorectal or endometrial cancer who are first degree relatives of each other and one a first degree relative of consultant</li> <li>two affected first degree relatives (one less than 55 yrs)</li> </ul> <p>( C - Evidence level IV)</p>	<ul style="list-style-type: none"> <li>single colonoscopy if normal findings</li> <li>single repeat colonoscopy</li> </ul> <p><i>Incomplete colonoscopy should be followed by a barium enema</i></p> <p>( C - Evidence level IV)</p>	30 - 35 yrs and again at 55yrs	
High Risk	<ul style="list-style-type: none"> <li>≥3 family members affected by CRC or ≥2 with CRC and one with endometrial cancer in ≥2 generations; one affected relative must be age ≤50 at diagnosis; one of the relatives must be a first degree relative of the other two.</li> <li>Gene carriers (HNPCC genes)</li> <li>Untested 1<sup>o</sup> relatives of gene carriers.</li> </ul> <p>( B - Evidence level III)</p>	<ul style="list-style-type: none"> <li>colonoscopy every 2 yrs</li> <li>discuss gynaecological screening for endometrial and ovarian cancer</li> <li>offer 2 yrly upper GI endoscopy for gastric cancer</li> <li>consideration needs to be given to other screening for other cancers which may occur in specific families and are part of the HNPCC spectrum</li> </ul> <p><i>Discuss prophylactic surgery for bowel and hysterectomy with bilateral oophorectomy For established colorectal and associated cancer discuss extent of surgery</i></p> <p>( B - Evidence level III)</p>	from 30 yrs of age or 5 yrs younger than the youngest affected  For stomach cancer from 50 yrs of age or 5 yrs younger than the youngest stomach cancer	70

- \* multiple polyps (3 or more adenomas) in an individual with one of the above criteria for medium and high risk may be regarded as 'affected'.
- \*\*Screening should be offered within a Managed Clinical Network with Colonoscopy performed by an accredited gastroenterologist or surgeon and barium enema by a Radiologist with a special interest in GI.
- \*\*\* a current relevant study for patients with CRC diagnosed at <55yrs is the COGS study co-ordinated by Mr Malcolm Dunlop
- \*\*\*\* the CAPP2 study co-ordinated by the Department of Medical Genetics at Newcastle upon Tyne is an intervention trial for individuals in HNPCC families

**Table 3: Summary of Referral and Screening Guidelines for Ovarian Cancer**

<i>Risk Level</i>	<i>Criteria for referral and Screening (Grade of recommendation)</i>	<i>Screening (Grade of recommendation)</i>	<i>Age to begin</i>	<i>end</i>
Low Risk	<ul style="list-style-type: none"> <li>anyone not fulfilling medium or high risk criteria</li> </ul> <p>( B - Evidence level III)</p>	<ul style="list-style-type: none"> <li>Reassure/Healthy Life Style</li> <li>Return to GP's care</li> </ul> <p>( B - Evidence level III)</p>		
Medium Risk	<ul style="list-style-type: none"> <li>two or more 1<sup>st</sup> or 1<sup>st</sup> and 2<sup>nd</sup> degree relatives with OvCa</li> <li>two 1<sup>st</sup> or 1<sup>st</sup> and 2<sup>nd</sup> degree relatives with OvCa at any age or BrCa diag under 50yrs;</li> <li>One OvCa and two breast cancers diagnosed less than 60 yrs on same side of family in 1<sup>st</sup> degree relatives or 2<sup>nd</sup> degree via a male</li> <li>two 1<sup>st</sup> or 2<sup>nd</sup> degree relative with CRC and an endometrial Ca and one with OvCa;</li> <li>one affected relative with OvCa and HNPCC family history;</li> </ul> <p><i>At least one case of ovarian cancer in each category</i></p> <p>( C - Evidence level IV)</p>	<ul style="list-style-type: none"> <li>Appointment with a Gynaecol</li> <li>Vaginal U/S – yearly</li> <li>Ca 125 – yearly</li> <li>Discussion of prophylactic oophorectomy</li> <li>UKCCCR Trial</li> <li>Additional relevant screening <b>may</b> be offered for women in the latter two groups</li> </ul> <p>( C - Evidence level IV)</p>	35 yrs or 5 yrs younger than the youngest case - <b>yearly</b>	65
High Risk	<ul style="list-style-type: none"> <li>an individual in family with BRCA1, BRCA2, hMLH1, hMSH2 or other predisposing gene;</li> <li>untested 1<sup>o</sup> relatives of gene carriers;</li> <li>1<sup>o</sup> relative with breast and ovarian cancer.</li> </ul> <p><i>At least one case of ovarian cancer in each category</i></p> <p><i>Criteria designed to essentially fulfill the criteria of the UKCCCR National Familial Ovarian cancer Screening Trial</i></p> <p>( C - Evidence level IV)</p>	<ul style="list-style-type: none"> <li>Appointment with a Gynaecol/Oncologist</li> <li>Vaginal U/S – yearly</li> <li>Ca 125 – yearly</li> <li>Discussion of prophylactic oophorectomy</li> <li>Breast screening as above</li> <li>UKCCCR Trial</li> </ul> <p>( C - Evidence level IV)</p>	35 yrs or 5 yrs younger than the youngest case - <b>yearly</b>	65

## **APPENDIX 1**

### **REFERRAL GUIDELINES FOR FAMILY HISTORY OF BREAST CANCER**

A family should contain:

- One first degree relative with bilateral breast cancer or breast and ovarian cancer;
- or**
- One first degree relative with breast cancer diagnosed under age 40 years or one first degree male relative with breast cancer diagnosed at any age;
- or**
- Two first or first and second degree relatives with breast cancer diagnosed under age 60 years and/or ovarian cancer at any age on the same side of the family;
- or**
- Three first or second degree relatives with breast or ovarian cancer on the same side of the family (always one 1<sup>st</sup> degree relative unless history is via father)
- or**
- An individual with BRCA 1 or BRCA 2 mutations or other known predisposing gene mutations.

*In this context a first degree female relative is mother, sister or daughter. A second degree relative is grandmother, granddaughter, aunt or niece.*

SIGN does not broadly define high risk. Agreed to include high risk individuals as including:

- Gene carriers (BRCA1, BRCA2, p53, pTEN)
- Untested 1<sup>o</sup> relatives of gene carriers
- First degree relatives of an affected (or 2<sup>o</sup> via intervening male relative) in a family with 4 or more relatives with breast cancers (bilateral breast cancer being counted as 2) or ovarian or male breast cancer at any age in three generations
- One first degree relative (or second via an intervening male relative) with breast and ovarian cancer.

## APPENDIX 2

### REFERRAL GUIDELINES FOR A FAMILY HISTORY OF OVARIAN CANCER

A family should contain: \*

- Two or more 1<sup>st</sup> or 1<sup>st</sup> and 2<sup>nd</sup> degree relatives with Ovarian Cancer  
**or**
- Two 1<sup>st</sup> or 1<sup>st</sup> and 2<sup>nd</sup> degree relatives with OvCa at any age and BrCa diag under 50yrs  
**or**
- One OvCa and two breast cancers diagnosed less than 60 yrs on the same side of the family in first degree relatives or second degree via a male.  
**or**
- Two first or second degree relative with colorectal cancer and/or endometrial Cancer and one with Ovarian Cancer;  
**or**
- One affected relative with ovarian cancer and HNPCC family history;  
**or**
- An individual with BRCA 1 or BRCA 2 mutations or other known predisposing gene mutations.

*\*All affected individuals with breast and/or ovarian cancer should be first or second degree relatives of each other, and one should be first degree relative of referred patient and there should be at least one case of ovarian cancer in each category*

A family is deemed to be at high risk if the history includes :

- Gene carriers (BRCA1, BRCA2, hMLH1, hMSH2 etc)
- Untested I<sup>o</sup> relatives of gene carriers
- One first degree relative with breast and ovarian cancer

*Criteria designed to fulfill the criteria of the UKCCCR National Familial Ovarian cancer Screening Trial*

### **APPENDIX 3**

#### **REFERRAL GUIDELINES FOR A FAMILY HISTORY OF COLORECTAL CANCER (CRC).**

A family should contain :

- One relative with CRC under age 45 years,
- Two affected with colorectal cancer (one less than 55yrs) who are first degree relatives of each other and one a first degree relative of consultand
- 3 affecteds with colorectal or endometrial cancer who are first degree relatives of each other and one a first degree relative of consultand
- or two affected first degree relatives ( one less than 55yrs)
- A family history compatible with HNPCC (Amsterdam criteria)
  - People with a family history compatible with HNPCC ( $\geq 3$  family members affected by CRC or  $\geq 2$  with CRC and one with endometrial cancer in  $\geq 2$  generations; one affected relative must be aged  $\leq 50$  at diagnosis; one of the relatives must be a first degree relative of the other two).

#### **High Risk Individuals include:**

- $\geq 3$  family members affected by CRC or  $\geq 2$  with CRC and one with endometrial cancer in  $\geq 2$  generations; one affected relative must be age  $\leq 50$  at diagnosis; one of the relatives must be a first degree relative of the other two.
- Gene carriers (HNPCC genes)
- Untested 1<sup>o</sup> relatives of gene carriers.

## **APPENDIX 4**

### **HIGH RISK CRITERIA**

#### **Breast :**

A family is deemed to be at high risk includes :

- Gene carriers (BRCA1, BRCA2, p53, pTEN, etc)
- Untested I° relatives of gene carriers
- I° relatives of an affected (or 2° via intervening male relative) in a family with 4 or more breast cancers (bilateral breast cancer counting as two cancers) or ovarian cancers or a male breast cancer in three generations
- or 1° relative with breast and ovarian cancer.

#### **Ovarian cancer:**

High risk:

- an individual in family with BRCA1, BRCA2, hMLH1, hMSH2 or other predisposing gene;
- untested I° relatives of gene carriers;
- 1° relative with breast and ovarian cancer

*At least one case of ovarian cancer in each category*

#### **Colorectal cancer**

A family is deemed to be at high risk when the family history is compatible with HNPCC (Amsterdam criteria) :

- $\geq 3$  family members affected by CRC or  $\geq 2$  with CRC and one with endometrial cancer in  $\geq 2$  generations; one affected relative must be aged  $\leq 50$  at diagnosis; one of the relatives must be a first degree relative of the other two.
- Gene carriers (HNPCC genes)
- Untested I° relatives of gene carriers.

**APPENDIX 5 : Discussion Points for Breast and Ovarian Cancer**

NAME:	STUDY NUMBER:
<b>Discussion at clinic visit for Breast</b>	<b>Appointment Date</b>
Genetic Risk	
Family Genetic Risk	
Breast Cancer Testing	
Healthy Lifestyles	
Oral Contraception Pill	
Hormone Replacement Therapy	
IBIS or successor	
Breast Self Examination	
Others	
Screening Recommendations	Clinical Examination Date  Mammography Due
Awaiting information on for Cancer Registry	

**APPENDIX 6: Discussion Points for Colorectal Cancer**

NAME:	STUDY NUMBER:
<b>Discussion at clinic visit for Bowel</b>	<b>Appointment Date</b>
Genetic Risk	
Family Genetic Risk	
Gene Testing	
Healthy Lifestyles	
Family member who could supply DNA	
Patient will discuss with relative	YES NO
Patient will supply Patients Name, Address and GP's name and Address	Will Send Will Call Dept
Information Received	Date
Information sent to	Patient Date GP
Screening Recommendations	Colonoscopy YES NO Date of For referral to for colonoscopy
Awaiting information on for Cancer Registry	

## Appendix 7

### **GUIDELINES FOR PEOPLE GENETICALLY PREDISPOSED TO BREAST AND OVARIAN CANCER**

#### ***Breast Cancer***

Breast cancer is the most common form of cancer among women in Scotland and the second most common cause of death from cancer in women. In 1994, 3,058 cases of breast cancer were diagnosed in women and there were 1,275 deaths from this disease. The lifetime risk to women of developing breast cancer is about 8%. Breast cancer differs significantly from other common cancers in women in that a relatively high proportion of cases - about 22% in 1994 - occur among women under the age of 50. It is likely therefore that between 25% and 30% of all cases of breast cancer develop among women under 50. Breast cancer is the commonest cause of death among women aged 40-50.

About 5% of breast cancer cases are thought to be caused by highly penetrant germ-line mutations in dominant cancer predisposition genes including BRCA1 and BRCA2 [1-4]. Estimates of the lifetime penetrance of these genes differ. Some studies have estimated that carriers of the BRCA1 gene have a risk of 51% of developing breast cancer by the age of 50, rising to 85% by the age of 70. About 2% of all breast cancer cases are thought to be caused by this gene. It has been suggested that the BRCA2 gene may account for a similar proportion of cases as BRCA1.

The lifetime risk to all women in Scotland of developing breast cancer is 8%. If 5% of all cases are caused by highly penetrant genes, and if the average lifetime penetrance of these genes is 80%, then the prevalence rate of gene carriers in the general population is 5 per 1,000. If the lifetime penetrance of these genes is 50%, the prevalence rate increases to 8 per 1,000. These prevalence rates imply that there are between 13,000 and 21,000 carriers of highly penetrant breast cancer genes in the female population.

Breast cancers caused by known genetic mutations are likely to occur at an earlier age than cases of sporadic cancer. Among women in their 40s about 15% of breast cancers may be due to highly penetrant cancer predisposition genes, and among women in their 30s this proportion rises to about 20% [5]. Women with BRCA1 and BRCA2 mutations are at increased risk of other forms of cancer, especially of ovarian and colorectal cancer. They are also at high risk of contralateral breast cancer.

#### ***Family History (Medium Risk)***

Almost every study that has examined breast cancer risks has found significantly increased risk to female relatives of breast cancer patients. Although estimates vary, most of these studies have found that the risk to first degree relatives of a breast cancer patient is 2-3 times the general population risk. This relative risk increases to 3-4 if a woman has two first degree relatives with breast cancer or a first degree relative who developed breast cancer under the age of 45.

Highly penetrant genes probably account for a limited proportion of this observed familial risk. It is likely that most of the risk is accounted for by inherited predisposition genes of lower penetrance, though it is also possible that shared environmental and lifestyle factors contribute to some of the increased risk [6].

## Ovarian Cancer

Ovarian cancer is the fourth most common cause of cancer among women in Scotland, with 576 cases diagnosed in 1994. The lifetime risk to women of developing ovarian cancer is about 1.5%. The incidence of ovarian cancer increased by almost 9% during the 1980s. Ovarian cancer is often diagnosed at a late stage and as a result survival rates are poor. The 5 year survival rate is only 29% and there were 445 deaths from ovarian cancer in 1994. Survival rates have improved only slightly since the early 1970s.

As with breast and colorectal cancer, the evidence suggests that high penetrance cancer predisposing genes account for a small proportion (5%) of ovarian cancers, and that other less highly penetrant genes may also account for a significant proportion of cancer cases. The BRCA1 gene causes a predisposition to ovarian as well as breast cancer and it has been estimated to account for about 5% of ovarian cancers among women under 70 [7]. There is some evidence to suggest that this proportion may be higher in younger age groups [8].

### ***Family History (Medium Risk)***

Studies indicate that a first degree relative of a patient with ovarian cancer is at 2-3 times the general population risk of developing cancer. The risk is greater if a woman has two first degree relatives and if a first degree relative developed cancer at an early age. The relative risk is also influenced by the incidence of breast cancer in first degree relatives.

### **Referral guidelines for individuals with a family history of breast cancer**

- One first degree relative with bilateral breast cancer or breast and ovarian cancer; **or**
- One first degree relative with breast cancer diagnosed under age 40 years or one first degree male relative with breast cancer diagnosed at any age; **or**
- Two first or first and second degree relatives with breast cancer diagnosed under age 60 years or ovarian cancer at any age on the same side of the family; **or**
- Three first or second degree relatives with breast or ovarian cancer on the same side of the family.
- One first degree relative (or 2<sup>o</sup> via intervening male relative) with 4 or more relatives affected with breast cancer (bilateral breast cancer being counted as 2) breast cancer or ovarian or male breast cancer in three generations
- BRCA1 and BRCA2 gene carriers and their first degree relatives

*In this context a first degree female relative is mother, sister or daughter. A second degree relative is grandmother, granddaughter, aunt or niece.*

### **Referral guidelines for individuals with a family history of ovarian cancer. A family should contain: \***

- Two 1<sup>st</sup> or 1<sup>st</sup> and 2<sup>nd</sup> degree rel with Ovarian Cancer **or**
- Two 1<sup>st</sup> or 1<sup>st</sup> and 2<sup>nd</sup> degree rel with OvCa at any age or BrCa diag under 50yrs **or**
- One OvCa and two breast cancers diagnosed less than 60 yrs on same side of family in 1<sup>st</sup> degree relatives or 2<sup>nd</sup> degree via a male
- Two first or second degree relative with colorectal cancer and/or endometrial Cancer and one with Ovarian Cancer **or**
- One affected relative with ovarian cancer and HNPCC family history; **or**

An individual with BRCA 1, BRCA 2, hMLH1 or hMSH2 mutations or other known predisposing gene mutations.

- untested 1<sup>o</sup> relatives of gene carriers;
- 1<sup>o</sup> relative with breast and ovarian cancer

*\*All affected individuals with breast and/or ovarian cancer should be first or second degree relatives of each other, and one should be first degree relative of referred patient and in each category, one first or a second via the father affected with ovarian cancer.*

*At least one case of ovarian cancer in each category*

*At least one case of ovarian cancer in each category*

### **Management of 'At Risk' Individuals**

#### **Low Risk**

- Reassurance/Healthy Life Style
- If breast cancer FH, letter and leaflet on Breast Awareness for female patients.
- Return to GP's care

#### **Medium Risk**

- Counselling
- Screening

#### **Breast**

- Mammogram ( and U/S as appropriate) – optimally at Breast Screening
- Physical Examination by Breast Clinician yearly.

Optimally all breast screening should be offered in an appropriately quality controlled environment with highly trained radiographers and radiologists. This situation clearly describes that available within the National Breast Screening Unit for women over 50 years of age.

Screening recommendations will be for breast screening from 35 to 40 years of age 2 yearly and from 40 to 50 years 1 yearly, or from 5 years younger than the youngest woman affected in the family, but not younger than 35 years or older than 40 yrs, until they reach 50 years of age and enter the National Screening Programme. Screening should be by mammography as above, one yearly physical examination of the breasts by a breast surgeon, and discussion and advice on where to obtain information on breast awareness. (See "Education")

**Ovary** - from 35 years of age or 5 years younger than the youngest affected in the family until 65 years.

- Appointment with an appropriate clinician
- Vaginal U/S – yearly
- Ca 125 – yearly
- Discussion of prophylactic oophorectomy
- UKCCCR Trial

Screening should appropriately be co-ordinated by a clinician with a special interest in ovarian cancer. This should include ultrasound and Ca 125 estimation on one yearly basis. Women with a family history of both breast and ovarian cancer, women with a family history of ovarian cancer alone and women with a family consistent with HNPCC with ovarian cancer in the family should be entered into the UKCCCR trial.

**HIGH RISK** - Counselling  
- Screening

### **Breast**

- Mammogram (and U/S as appropriate– optimally at Breast Screening Center yearly.
- Physical Examination by Breast Clinician yearly.

Breast screening in such women should be annually from 25 years of age in gene carriers or from 5 years younger than the youngest affected in the family (but not younger than 25yrs or older than 35 yrs) until 40 yrs at 2yearly intervals and from 40 to 50 years at 1 yearly intervals then eighteen monthly from 50 to 64 within the National Screening Programme and 3 yearly thereafter. Physical examination 1 yearly from 25 years until 64 years.

**Ovary** - from 35 years or 5 yrs younger than the youngest affected in the family to 65 years.

- Appointment with Gynaecologist
- Vaginal U/S – yearly
- Ca 125 – yearly
- Discussion of prophylactic oophorectomy
- UKCCR Trial

Prophylactic surgery (oophorectomy) should be discussed with high risk individuals Screening for other cancers should be considered depending of the family history. Women should be informed of the limitations of current forms of ovarian screening.

Women with a family history of both breast and ovarian cancer, women with a family history of ovarian cancer alone and women with a family consistent with HNPCC with ovarian cancer in the family should be entered into the UKCCR trial.

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## Appendix: 8: SURVEILLANCE GUIDELINES FOR PEOPLE GENETICALLY PREDISPOSED TO COLORECTAL CANCER

### *Background and Rationale*

#### *Colorectal cancer risk and family history*

Colorectal cancer is common and so family history of the disease is also common. The population prevalence of *any* family history of CRC is 4-7% in control cohorts recruited to published studies, suggesting that ~100,000 Scots aged 30-70yrs have an affected close relative. From published systematic data, there are an estimated 12,000 Scots aged 30-70yrs with a “high risk” family history (2 affected first degree relatives or 1 aged <45yrs), equating with an empirical >1:10 lifetime colorectal cancer risk.

There are three reasons for aggregation of cancer cases within families; shared genes, shared environment and chance. However, prospective cohort studies and case-control studies on colorectal cancer occurrence in relatives provide substantial evidence for a genetic input. Colonoscopic studies also demonstrate an excess of benign and malignant neoplasms in relatives of affected patients. Some genes impart a high risk, others have a more minor effect. Overall, the relative risk is ~2 for members of families with *any* colorectal cancer cases and this risk increases with the degree of family history (Table 1).

**Table 1**

Degree of FH	Relative risk				
	<i>Houlston (lifetime risk)*</i>	<i>St John (OR)</i>	<i>Fuchs (RR)</i>	<i>Slattery (OR)</i>	
Any FH	1:17	1.8	1.72	2.15 (m)	2.43 (f)
Affected relative <45yrs	1:10	3.7	N/A	3.61(m)**	7.18 (f)
Two affected relatives	1:6	5.7	2.75	9.24 (m)	5.00 (f)

\*Derived from data collected in 1970. \*\*Affected relative aged<50yrs

Risk expressed as a relative risk is not well suited to clinical use. Table 2 presents risks in a clinically more useful manner and shows cancer risk *over the next 10 years* along with risks associated with biannual colonoscopy for patients of different ages with a “high risk” family history (2 affected 1<sup>o</sup> relatives or 1 affected aged <45yrs).

**Table 2**

Age now	Colon cancer risk in next 10 years		Chance of biannual colonoscopy preventing death in “high risk” group	Risk of harm from biannual colonoscopy	
	<i>“High risk” family history</i>	<i>Population risk</i>		<i>Morbidity</i>	<i>Mortality</i>
30	0.20%	0.03%	0.11%	1.2%	~0.1%
40	0.99%	0.17%	0.55%	1.2%	~0.1%
50	1.15%	0.57%	0.64%	1.2%	~0.1%
60	2.78%	1.37%	1.20%	>1.2%	>0.1%
70	5.00%	3.00%	2.40%	>1.2%	>0.1%

#### *Colonic surveillance in people with a “high risk” family history*

There are no randomized trials of colonic surveillance in groups defined by family history, even for people at the highest risk. Hence, there are no conclusive data on which to base recommendations for surveillance. There are two non-randomized, comparative studies of surveillance in HNPCC families. Both *suggest* survival benefit. In current practice, many people are recommended surveillance because of a “high risk” family history. However, there are appreciable risks associated with colonoscopic surveillance. Furthermore, incomplete colonoscopy may miss tumours (~5%). The serious complication rate (mainly perforation) is ~1/300 -1/500 and mortality ~1/6,000 procedures. These rates comprise what might be expected in “high risk” cohorts undergoing a mix of surveillance and therapeutic colonoscopies. Iatrogenic risks are additive for repeat procedures. The absolute risk of biannual colonoscopy over 10 years is shown in Table 2, serving to emphasize the need to balance *absolute* risk and benefit of long term surveillance.

***Hereditary non-polyposis colorectal cancer (HNPCC) and DNA mismatch repair genes***

People from families fulfilling HNPCC criteria are at 50% risk of being a gene carrier while people shown to carry a DNA mismatch repair gene mutation have a very high risk of colorectal cancer. The former have a 30% sex-average lifetime risk and the latter a 60% risk. Hence the rationale in offering biannual colonoscopy, notwithstanding the lack of randomized trial data. There is also an *additional* excess risk of other cancers: 40% - endometrial, 10% - ovarian, 20% - gastric, and other tumours where the risk is lower.

**PRAGMATIC GUIDELINES FOR MANAGEMENT AND SURVEILLANCE OF PEOPLE AT GENETIC RISK OF COLORECTAL CANCER**

In the absence of firm data on efficacy of screening genetically predisposed individuals, these are pragmatic guidelines using available data which balance risks against benefits of surveillance and take account of available Health Service resources.

**PEOPLE WHO SHOULD BE REFERRED TO REGIONAL CLINICAL GENETICS SERVICE**

- People with a family history compatible with HNPCC ( $\geq 3$  family members affected by CRC or  $\geq 2$  with CRC and one with endometrial cancer in  $\geq 2$  generations; one affected relative must be aged  $\leq 50$  at diagnosis; one of the relatives must be a first degree relative of the other two).

People with :

- 1 relative affected by colorectal cancer when aged <45yrs;
- 2 (one affected less than 55yrs) or 3 affecteds with colorectal and/or endometrial cancer who are first degree relatives of each other and one a first degree relative of consultant
- or two affected first degree relatives ( one less than 55yrs at diagnosis).

**SURVEILLANCE FOR PEOPLE FROM HNPCC FAMILIES (MUTATION STATUS UNKNOWN) AND PEOPLE WITH DNA MISMATCH REPAIR GENE MUTATIONS**

***Colon cancer - lifetime risk to gene carriers 80% male ~30% female***

- **Colonoscopy every 2 years** - from 30 yrs of age or from 5 yrs younger than the first case in family until aged 70yrs.
- **Discuss prophylactic surgery** - especially if recurrent polyps. Colectomy and ileorectal anastomosis best option

- **Patients undergoing surgery for established colorectal cancer** - Require more extensive resection to reduce risk of metachronous tumour. Colonic tumour best treated by colectomy and ileorectal anastomosis, rectal cancer usually would include an extensive left hemi-colectomy with anterior resection

**Endometrial and ovarian cancer - lifetime risk to gene carriers 40% and 10% respectively**

- **Discuss annual gynaecological screening** - There is no established method for endometrial cancer screening and no available data on efficacy. Some centers offer clinical examination, transvaginal ultrasound and pipelle endometrial biopsy. Experience in familial ovarian cancer indicates ovarian screening is of doubtful efficacy. There is a good case to avoid screening outwith research studies
- **Discuss prophylactic hysterectomy and bilateral oophorectomy** - Should be done by a gynaecologist and full pre-operative discussion of surgical risks/potential benefits is essential. There is no clear evidence for benefit, but surgery may be preferable to pelvic screening for women past reproductive age, particularly if there is a history of gynaecological cancer in the family

**Gastric cancer - lifetime risk to gene carriers ~20%**

- **Offer 2 yrly upper GI endoscopy, contemporaneous with colonoscopy** - aged >50yrs or 5 yrs younger than the first case in family. No available data on benefit, so a good case to recommend no screening outside trials

**Others**

- Consideration may need to be given to other screening for other cancers which may occur in specific families and are part of the HNPCC spectrum

**SURVEILLANCE FOR GROUPS DEFINED BY EMPIRICAL RISK ASSESSMENT**

**People with 1 affected first degree relative aged >45yrs or 1 first and 1 second degree relative**

- **Reassure** - encourage recruitment to population screening if available and early attendance with symptoms

**People with 2 or 3 affecteds with colorectal or endometrial cancer who are first degree relatives of each other/ or 2 affected first degree relatives/ or 1 relative aged <45yrs**

- **Single colonoscopy at 35yrs or aged >30yrs if concerned. If clear, repeat screen at 55yrs** - This is the most controversial area but absolute risks are not in favour of biannual colonoscopy (Table 2). The chance of biannual colonoscopy preventing cancer death is less than the risk of serious complication for people of all but the oldest age groups. Biannual colonoscopy is recommended in several screening policies and is current practice of some clinicians, but would generate very large numbers of procedures. However, the absolute 10-year cancer risk for a person aged 50 with 2 affected first degree relatives is 1.15%, whereas the population risk at age 70yrs is 3%. Thus, colonoscopic screening of the elderly could be more effective than screening people fulfilling "high risk" family history criteria. These guidelines accord with a recent consensus paper of US expert opinion<sup>23</sup>.

**NOTES Incomplete colonoscopy should be followed by a barium enema, preferably at the same hospital attendance.**

**Close liaison between regional genetic centers and gastroenterologists/gynaecologists involved in screening is essential.**

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## **APPENDIX 9**

### **Minimum dataset for cancer family clinics**

1. Identifier applied to this individual and to this family : Pedigree number and individual number (CHI number)
2. Date and place of birth,
3. NHS number, CHI number
4. Ethnicity
5. GP
6. Home address (postcode).
7. Telephone number.
8. Source and route of referral (e.g. from GP, initiated by affected relative).
9. Employment,
10. Previous cancers
11. Symptomatic – yes/no.
12. Family history confirmed – yes/no.
13. Blood or DNA obtained – yes/no. Consent – yes/no. Where stored.
14. Mutation found in family – yes/no.
15. Presymptomatic testing – yes/no/?
16. Cyrillic pedigree drawn – yes/no.
17. What investigations? Results?
18. Referral to other clinic – yes/no (e.g. Surgical, Gynaecology, Psychology, Other).
19. Primary physician.
20. When screening started? – Type? Response?
21. Entered into any trials – yes/no (State which trial).
22. Annual review date. Screen outcome.
23. Cancer diagnosis – yes/no. When?  
How presented (detected at planned screening?)  
Site? Stage?  
Pathological findings?  
Treatment?  
Outcome on F/U?

*Proformer provided to assist in ensuring all data possible is collected*

## APPENDIX 9 - MINIMAL DATA SET

<b>SURNAME:</b>	<b>UNIT NUMBER:</b>
<b>FIRST NAME:</b>	<b>GENETIC UNIT NUMBER:</b>
<b>OTHER NAMES:</b>	<b>PEDIGREE NUMBER:</b>
<b>NAME AT BIRTH:</b>	<b>CHI NUMBER:</b>
ADDRESS:	Date of Birth:     /     /
	Place of Birth:
POSTCODE:	MALE / FEMALE
Tel. Number:	Employment:
CGU Consultant:	Ethnicity

### GP's DETAILS

GP's Name:	
GP's Address:	

### REFERRAL DETAILS

Referred by:	
Speciality:	Hospital:
Referral date:	
Family History Confirmed:	YES / NO
Cyrillic pedigree drawn:	YES / NO

**SYMPTOMATIC**     **YES / NO**

### INVESTIGATIONS

Blood or DNA obtained: <b>YES / NO</b>	Consent Given: <b>YES / NO</b>
Where stored:	
Mutation found in family:	YES / NO
Presymptomatic testing:	YES / NO

### MANAGEMENT

When screening started:	Screen outcome: (Continue overleaf if nec.)
Entered into any trials: <b>YES / NO</b>	
Which? :	
What investigations:	What results:
Referral to Other Clinic:	
Annual review date:	

### PERSONAL HISTORY

Previous Cancers:		
Cancer diagnosis: <b>YES / NO</b>	Type:	When? :
How presented:		
Site:	Stage:	
Path. No:	Pathological Findings: (continue overleaf if nec.)	
Treatment:	Outcome on F/U:	

## Referral Guidelines Audit

**Column 1:** Tick **ONE** box which most closely matches details in referral letter.

**Column 2:** Tick **ONE** box which most closely matches family history when completed and confirmed.

### **BREAST**

- | <b>1</b>                 | <b>2</b>                 |   |
|--------------------------|--------------------------|---|
| <input type="checkbox"/> | <input type="checkbox"/> | One first degree relative with bilateral breast cancer or breast and ovarian cancer   |
| <input type="checkbox"/> | <input type="checkbox"/> | One first degree relative with breast cancer diagnosed before forty years of age <b>or</b> one first degree male relative with breast cancer at any age       |
| <input type="checkbox"/> | <input type="checkbox"/> | Two first degree <b>or</b> first and second degree relatives with breast cancer diagnosed before sixty years of age <b>and / or</b> ovarian cancer at any age |
| <input type="checkbox"/> | <input type="checkbox"/> | Three first or second degree relatives with breast or ovarian cancer  |
| <input type="checkbox"/> | <input type="checkbox"/> | Known BRCA1 or 2 (or other cancer gene mutation) in family  |
| <input type="checkbox"/> | <input type="checkbox"/> | Other (i.e. none of the above)  |

### **OVARIAN**

- |                          |                          |   |
|--------------------------|--------------------------|---|
| <input type="checkbox"/> | <input type="checkbox"/> | Two or more relatives with ovarian cancer (first degree <b>or</b> first and second degree)  |
| <input type="checkbox"/> | <input type="checkbox"/> | One relative with ovarian and one with breast cancer diagnosed before fifty years of age (first degree <b>or</b> first and second degree) |
| <input type="checkbox"/> | <input type="checkbox"/> | One relative with ovarian and two with breast cancer diagnosed before sixty years of age (first degree <b>or</b> first and second degree) |
| <input type="checkbox"/> | <input type="checkbox"/> | Two relatives with CRC or endometrial cancer and one with ovarian cancer (first degree <b>or</b> first and second degree)                 |
| <input type="checkbox"/> | <input type="checkbox"/> | One relative with ovarian cancer and HNPCC FH   |
| <input type="checkbox"/> | <input type="checkbox"/> | Known BRCA1 or 2 (or other cancer gene mutation) in family  |
| <input type="checkbox"/> | <input type="checkbox"/> | Other (i.e. none of the above)  |

### **CRC**

- One first degree relative with CRC diagnosed before forty-five years of age
- Two first degree relatives with CRC
- Family History of CRC fulfilling Amsterdam criteria (three or more relatives with CRC **or** two or more relatives with CRC and one relative with endometrial cancer in two or more generations, one diagnosed before fifty years of age, all related via first degree)
- Known HNPCC mutation or FAP mutation in family
- Other (i.e. none of the above)

### **OTHER CANCERS**

- e.g. complicated not fulfilling any of the above categories

### **CYRILLIC RISK**

At referral  At completion

## **APPENDIX 10**

### ***Evaluation - Extract from Report of the Priority Areas Cancer Team/Genetics Sub-Committee of the Scottish Cancer Co-ordinating and Advisory Committee: Cancer Genetics Services in Scotland.***

There are many aspects of the proposed system of screening people at significantly increased risk of breast, colorectal and ovarian cancer that are uncertain, and it is essential that the clinical and cost-effectiveness of these services should be subject to thorough evaluation. A detailed and comprehensive programme for evaluation should be drawn up and implemented within an agreed national framework.

The main issues that need to be evaluated include the following:

- (a) The effectiveness of the guidance and support provided to primary care. For many people concerned that they may be at increased familial risk of cancer, the first point of contact will be with primary care, and it is important that the guidance and support provided to primary care staff enables them to make a proper initial assessment of risks and to avoid inappropriate referrals to genetics clinics.
- (b) The effectiveness of genetics associates (or genetics nurses) in providing appropriate support to primary care and in assessing the risk of referred individuals.
- (c) The effectiveness of screening programmes in detecting cases of cancer. This will require monitoring of the number of cancers detected per 1,000 patients screened, and the number of interval cancers occurring among the screened population, and the false positive rate. This monitoring information should be done within different age bands so that an assessment can be made of the appropriateness of the age ranges covered by the screening and the screening frequency.
- (d) The appropriateness of the criteria used to assess people at medium or high risk on the basis of their family history. A relatively low detection rate (along with other criteria) may suggest that the family history criteria need to be reviewed.
- (e) The risk of complications associated with the screening procedures, especially the risks associated with colonoscopy.
- (f) The effects of screening programmes on mortality rates. This is a crucial measure of the effectiveness of screening of individuals at increased risk of cancer.
- (g) The effects of screening on anxiety levels in patients. It is important that the effectiveness of screening programmes in providing reassurance to people concerned about familial risks of cancer should be assessed.

The clinical and cost-effectiveness of the proposed screening programmes will need to be evaluated over a period of several years. Some aspects - for example, the effect on mortality rates - can only be evaluated over a long timescale. But other aspects may be evaluated within a shorter timescale. The essential requirement is that a clear and agreed programme of evaluation is established at the outset so that the proposed screening systems can be managed efficiently and effectively.

## **Data Collection**

### **Purposes of data gathering**

1. To facilitate running of the clinic – making appointments, identifying defaulters, “housekeeping”. (see Minimal Data Set)
2. To audit clinic activity.
3. To support clinical and laboratory research.

### **“Audit” questions that might be addressed through data analysis**

1. What is the demand for the clinical service? Is it changing?
2. What are the sources of referral? Are they changing?
3. What is the age, social, geographical profile of referred patients?
4. What is the risk profile of referred patients?
5. In what proportion of cases are specific management decisions taken – discharge, follow-up screening, MRI, IBIS, prophylactic surgery, referral to another clinic?
6. What is level of compliance with above? How often are invasive investigations (FNA/biopsy) undertaken?
7. What molecular studies are being undertaken, with what results?
8. What is the outcome in those who subsequently develop cancer? Are they diagnosed at an earlier stage? Is there a change in prognosis and survival?
9. What are the costs associated with different components of the clinical service?

### **The following “research” questions will also require interrogation of a clinic database.**

1. How many families are listed with given cancer patterns (e.g. 4 or more breast cancers on same side, presenting under age 60: multiple breast cancers plus at least one ovarian: those that include male breast cancers)?

2. How do rates of mutation detection or of cancer incidence relate to risk estimates?
3. Are there recurring BRCA1 or BRCA2 mutations in Scotland? If so, what patterns of cancer are associated with these?
4. Are there multi-cancer families (with breast and other cancers) without BRCA1 or BRCA2 mutations that might be suitable for linkage analysis to detect new cancer genes? If so, are there any clinical or pathological characteristics that help define homogeneous groups?
5. What impact does our clinical practice have on cancer morbidity and mortality? I.e. how many “early” cancers are detected by screening young patients? What is their long-term outcome? How does this compare with prophylactic surgery or chemoprevention? What is the relationship between risk estimate and optimal management?
6. What impact does mutation detection have on clinical practice? Should the nature of the mutation influence management decisions?

“Housekeeping,” audit and research questions will all require a common core of data, with additional information contributing to each area of interest. It would make sense to avoid multiple data entry so that a single database with several fields (some of which would be optional) ought to be the most efficient option. Cyrillic, with dynamic links to a relational database, has great potential advantages since, for almost all genetics clinics a family tree is an essential part of the record. Additional information can be fed into the various fields through the Cyrillic “front end” but can be retrieved and analysed via the relational database. Further developments in databases are required .

# Appendix 11

## Alternative Strategies for collecting Family History

### First degree relatives

Tick box if affected and enter approximate age at diagnosis

	Ovarian <input type="checkbox"/> Other <input type="checkbox"/> CRC <input type="checkbox"/> Breast <input type="checkbox"/> <b>Mother</b>	Ovarian <input type="checkbox"/> Other <input type="checkbox"/> CRC <input type="checkbox"/> Breast <input type="checkbox"/> <b>Father</b>		
Ovarian <input type="checkbox"/> Other <input type="checkbox"/> CRC <input type="checkbox"/> Breast <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<b>1 Sisters</b> 2 3 4 5	<b>Index</b>	<b>Brothers</b> 1 2 3 4 5	Other <input type="checkbox"/> CRC <input type="checkbox"/> Breast <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
	<b>Children</b> 1 2 3 4 5	Ovarian <input type="checkbox"/> Other <input type="checkbox"/> CRC <input type="checkbox"/> Breast <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
	No. of first degree relatives Ovarian Cancer <input type="checkbox"/> CRC <input type="checkbox"/> Breast Cancer <input type="checkbox"/> Other <input type="checkbox"/>			

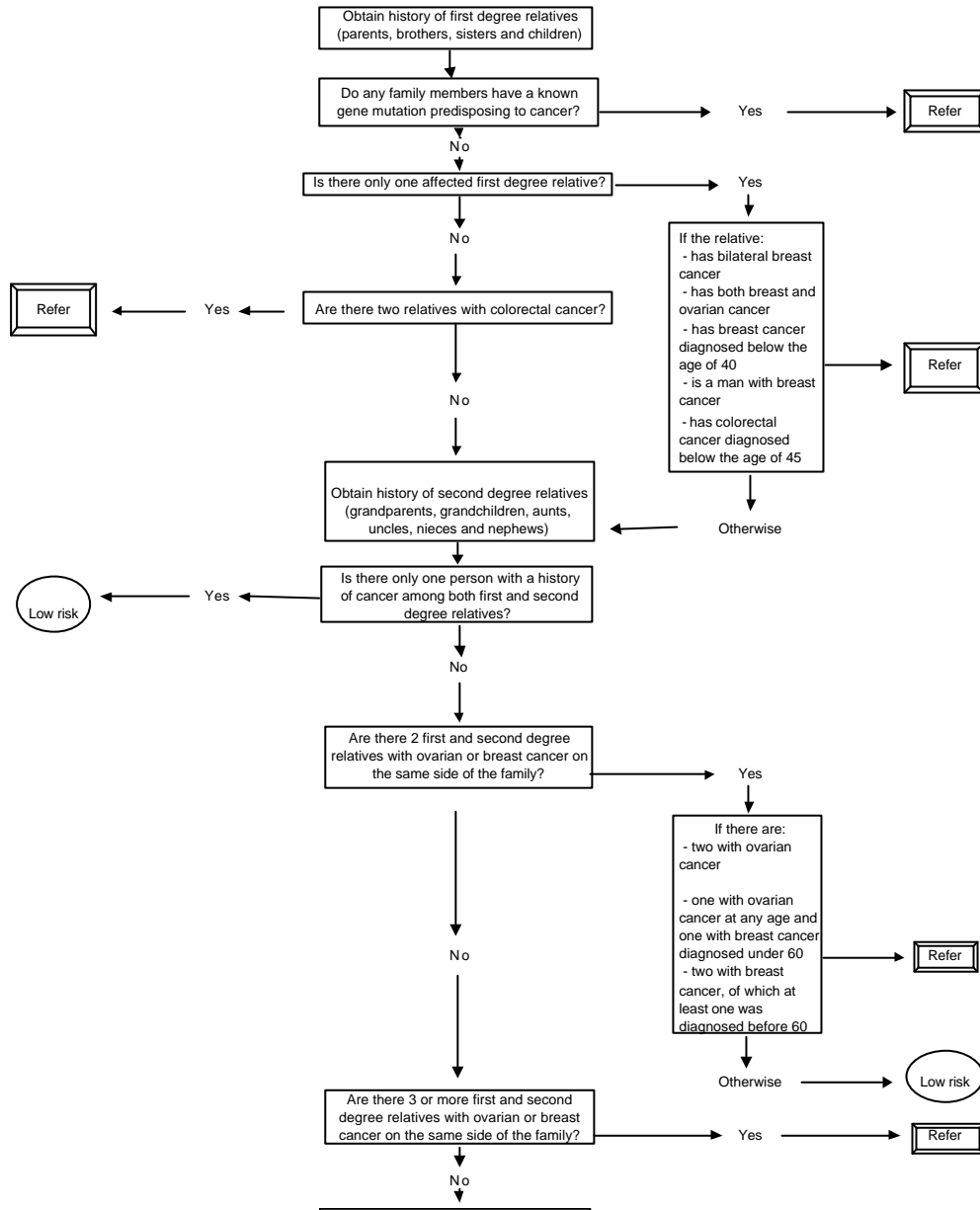
### Second degree relatives

Tick box if affected and enter approximate age at diagnosis

	Ovarian <input type="checkbox"/> Other <input type="checkbox"/> CRC <input type="checkbox"/> Breast <input type="checkbox"/> Maternal Grandmother Maternal Grandfather	Ovarian <input type="checkbox"/> Other <input type="checkbox"/> CRC <input type="checkbox"/> Breast <input type="checkbox"/> Paternal Grandmother Paternal Grandfather	
Mothers brothers 1 2 3 4	<b>Mother</b>	<b>Father</b>	Fathers brothers 1 2 3 4
Mothers sisters 1 2 3 4	<b>Sisters</b>	<b>Index</b>	<b>Brothers</b>
Nephews 1 2 3	<b>Children</b> 1 2 3 4	Grandchildren 1 2 3 4	Nieces 1 2 3
Nieces 1 2 3	Total number of maternal second degree relatives Ovarian Cancer <input type="checkbox"/> CRC <input type="checkbox"/> Breast Cancer <input type="checkbox"/> Other <input type="checkbox"/>	No. of first degree relatives <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Total number of paternal second degree relatives Ovarian Cancer <input type="checkbox"/> CRC <input type="checkbox"/> Breast Cancer <input type="checkbox"/> Other <input type="checkbox"/>
	plus <input type="checkbox"/> = <input type="checkbox"/>		plus <input type="checkbox"/>

## Alternative Strategies to follow guidelines for referrals

Assessment of a patient concerned about a family history of breast, colorectal or ovarian cancer



**Appendix 12**

Dear

Your relative.....has been  
referred to.....at the.....

genetics counselling service to investigate the possibility of a family history of tumours. For the purpose of accurate counselling and appropriate screening it would be most helpful to review your medical records. Any information contained in the records will be used for this purpose only and we should like to reassure you that no information shall be disclosed other than relates directly to family history of tumours.

If you have no objection to allowing these notes to be reviewed, I should be grateful if you would complete the attached slip and return it to me in the enclosed pre-paid envelope.

Many thanks for your co-operation.

Yours sincerely

.....

I grant permission to release information from the Cancer Registry records of:

Name:.....

Address:.....

Date of Birth:.....Sex:.....

To:.....at the:.....genetics counselling

service for the purpose of assisting in counselling my relatives.

Signed:.....Date:.....

Scottish Cancer Intelligence Unit  
 Information & Statistics Division  
 Trinity Park House, South Trinity Road  
 Edinburgh, EH5 3SQ  
 Telephone: 0131 551 8016

**Request To The Scottish Cancer Registry For Information  
 About A Relative Of A Genetic Counselling  
 Clinic Patient**

Clinic Ref No.                      ISD Ref. No. ....  
 .....

Genetic Counselling Clinics should complete **Sections 1, 2 & 3**. ISD will return form with **Sections 4 & 5** completed.

(Sections 1 & 4) DETAILS OF RELATIVE		
Date of Birth and Surname are essential for this request, but please complete as many fields as possible in Section 1.		
	<u>(Section 1) Details from Genetic Clinic</u>	<u>(Section 4) ISD Check &amp; Comments</u>
DATE OF BIRTH	/ /	/ /
SURNAME		
Forename		
Maiden/First Surname		
Address at Diagnosis		
Postcode at Diagnosis		
Hospital		
Case Reference No.		
Start Date of Treatment		
Cancer Registration No.		
Tumour Site		
Tumour Type		
Histology Verified? YES / NO		

(Section 2) VITAL STATUS	
Is the person identified above alive?	YES */ NO                      Date of Death (if known)                      / /
Consent form provided?	YES / NO
<p><b>*If this person is alive</b>, requests for information should be accompanied by a consent form signed by him/her (or his/her legal guardian). The consent form should permit the release of information relating to cancer from medical records to the Genetic Counselling Clinic. The managing Consultant and General Practitioner should be informed by the Genetic Counselling Clinic about the release of data and both should be provided with a copy of the signed consent form. ISD should also receive a copy of the signed consent form.</p>	

<b>(Section 3) DETAILS OF PERSON REQUESTING INFORMATION</b>	- Please print or use work address label
Name _____	tel. no. _____
Designation _____	
Organisation/Address _____	
<b>Consultant Clinical Geneticist authorising request</b> ..... (Signature) Date: ..... (Please print name)	

<b>(Section 5) ISD Comments</b>	Date of Death Consent Form
Central Database Regional Registry GRO(S) Fiche.....	.....
Date Request Received Date Information Returned Actioning Officer	.....