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FORECEE – Female cancer prediction using cervical *omics* to individualise screening and prevention

Study protocol
Version 4
21 April 2017

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1. Aims of the Study

The FORECEE project is focused on the shared ambition of a group of leading European clinicians and researchers to promote women's health and prevent female cancers.

The radical advance we wish to see is the implementation of omics-based methods into wide scale clinical practice for the stratification and risk prediction of cancers that are specific to women (breast, ovarian, endometrial and cervical cancer). A critical factor in the prevention of cancer is access to the cell of origin. Cervical screening, through application of the Papanicolaou test (or Pap smear) and/or human papilloma virus (HPV) testing assesses which women are at risk of developing an invasive cervical cancer and would benefit from a preventive procedure (i.e. excision of the cervical area at risk).

Widespread introduction of the Pap test has reduced the incidence of cervical cancer. In sharp contrast, breast, endometrial and ovarian cancers continue to pose considerable challenges in terms of risk prediction. Access to the cell of origin for these cancers can only be achieved with fully invasive methods such as a random breast biopsy, a hysteroscopy and endometrial biopsy, or a laparoscopy under general anaesthesia. These options are not feasible for the general population and hence our ability to date to identify and stratify high-risk groups is severely restricted.

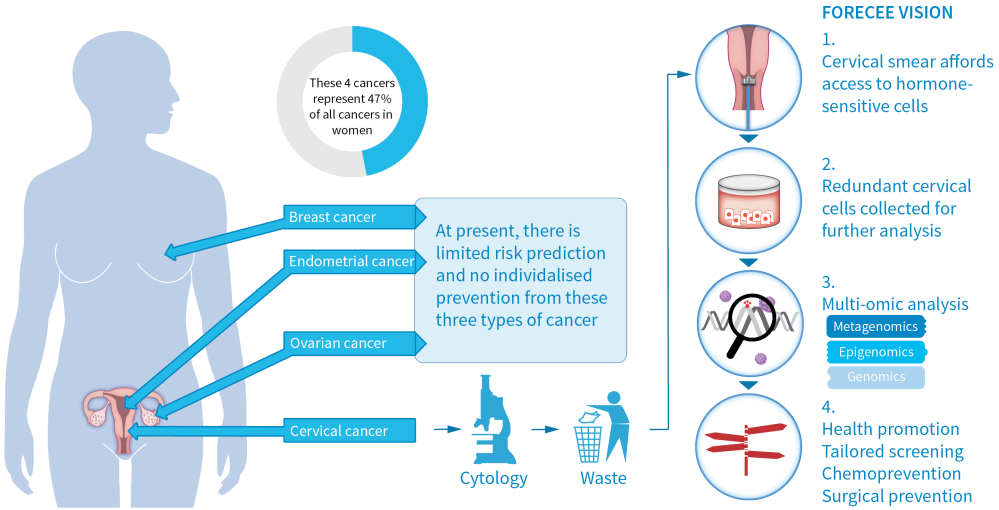

Fig 1. The FORECEE Vision – the use of cervical cells and omics-based analysis to predict the risk of all women-specific cancers

FORECEE's main purpose is to develop a tool based on genetic, epigenetic and microbiome changes in cervical cells, as well as buccal and blood samples, to aid prediction and risk stratification of the four main women-specific cancers: breast, ovarian, endometrial, and cervical cancer.

The principle aims of the study are listed below.

1. To identify minimally invasive biological markers that would aid the diagnosis of individuals at risk of breast, endometrial and ovarian cancer.
2. To identify molecular targets to prevent the development of breast and ovarian cancer.

2. Hypotheses

1. Women with a *BRCA* mutation have abnormal hormone regulation which leads to altered levels of estrogen and progesterone. In combination with normal hormonal events such as the menstrual cycle, this triggers changes in hormone-sensitive organs, which may subsequently be pre-disposed to cancer.
2. Systemic hormonal changes – as a function of exposure time – lead to epigenetic alterations (such as DNA methylation) in tissue-specific, hormone-sensitive cells, which can be used as a surrogate biomarker to identify women at risk of developing a cancer.
3. Steroid hormones (estradiol and/or progesterone) or genes regulated by these hormones (i.e., receptor activator of NF-κB ligand, RANKL) serve as targets for chemoprevention in *BRCA* mutation carriers.
4. Exfoliated tumour cells from ovarian cancer can be detected in the lavage fluid from the uterine cavity and proximal fallopian tubes.

3. Outcomes

1. Establishment of a biobank containing samples (buccal cells, cervical cells (endo- and ectocervical), endometrial cells, saliva, serum/plasma, white blood cells, urine, menstrual blood and various tissues removed during preventive or therapeutic surgery) and relevant epidemiological information from a cohort of women with a *BRCA1* or *BRCA2* mutation and age-matched women without a mutation.
2. Tools, based on a systems biology assessment of the epigenetic/hormonal data of the collected samples, to accurately predict the *BRCA* status without the need to do sequencing of the *BRCA* genes which can eventually be used as a simple screening tool for *BRCA* mutation carriers in the general population in order to identify those 50% of *BRCA* mutation carriers that currently would not be identified based on family history alone.
3. Insight into the systemic factors that lead to breast and ovarian cancer in *BRCA* mutation carriers in order to tailor preventive strategies.

4. Planned Analyses

We aim to recruit a total of 800 women with known *BRCA*/Lynch Syndrome-linked mutation and 1500 women with a confirmed absence of mutations in the relevant *BRCA*/Lynch Syndrome genes. Because of the higher prevalence of *BRCA* mutation carriers, these are envisaged to make up the majority of the participants.

Samples will be investigated as described below.

1. Analysis of hormone levels in plasma/serum and saliva of individuals with confirmed *BRCA* mutation and individuals with confirmed absence of *BRCA* mutations.
2. Genomic analysis (via advanced sequencing methods) and epigenomic analyses (DNA methylation, coding and non-coding RNA, chromatin modifications) in

various normal (cervical, buccal, peripheral and menstrual blood, breast, endometrium, ovary, Fallopian tube) and tumour (breast, endometrium and ovary) tissues.
3. Analyses of the genome, transcriptome and microbiome (16s RNA locus) of cells from cervix, endometrial lavage fluid and normal and abnormal tissue/blood products.
4. Cultivation of cells (i.e., menstrual blood stem cells, Fallopian tube, endometrium and ovarian surface cells) to confirm clinical data.
5. Long-term follow up (25 years) of these women with comparison of disease incidence and outcomes in both groups.

5. Background and Rationale

In the last 30 years, there has been little change in the UK mortality rates from ovarian cancer triple-negative (basal-cell) breast cancers and serous endometrial cancers. These cancers are more common in women with a *BRCA* mutation. In sharp contrast, cervical cancer mortality rates have been reduced by 75%. This dramatic success is due to (1) detailed understanding of cervical cancer development being triggered by the human papilloma virus (HPV), (2) successful development of tests to detect HPV where cervical cancer arises, (3) the advent of an effective vaccine against HPV, (4) that we are able to detect pre-invasive lesions using cytology taken from the transformation zone – the area where cervical cancer starts to develop – and, finally, (5) that we are able to prevent these lesions by a small surgical excision of this area.

Every day, 20 women are diagnosed with ovarian cancer in the UK. Of those, only 7 will survive beyond 5 years. About 5-10% of all breast and ovarian cancers, in particular those that are difficult to treat (high grade serous ovarian and triple-negative breast cancers), arise in women with a germline mutation in the *BRCA1* and *BRCA2* gene.

Women who carry heritable *BRCA1/2* gene mutation have up to a 60% lifetime risk of developing ovarian cancer and an up to an 85% lifetime risk of breast cancer. In the general population, the *BRCA* carrier rate is 1:400-800 women. Some populations are at higher risk, the largest of which is the Ashkenazi Jewish community (women of Jewish heritage whose families originate in the UK or mainland Europe). This population is thought to be at higher risk due to founder mutations, which have been preserved in the gene pool. The most recent estimates suggest that the Ashkenazi Jewish carrier rate of *BRCA* mutations is as high as 1:40.

Interdisciplinary work over several decades has provided compelling evidence that sex hormone levels play an important role in breast and ovarian cancer development. Surgical removal of the ovaries and Fallopian tubes reduces not only ovarian cancer risk but also breast cancer risk. The exact mechanism of this interaction remains to be fully understood.

More recently, our group has led a collaborative research effort to investigate whether healthy premenopausal *BRCA* mutation carriers have increased levels of oestrogen and progesterone compared to health non-mutation carriers. Recently, we tested the hypothesis that human *BRCA1* mutation carriers have a sex hormone dysregulation and altered end-organ hormone-sensitivity by comparing the endometrial thickness (as an index of hormone regulation) at specific time points during the menstrual cycle in 982 *BRCA* mutation carriers and non-carriers in our UK Familial Ovarian Cancer

Screening Study (UKFOCSS) and correlating the results with measurements of sex steroid hormone levels in the study subjects. The endometrial thickness was higher during the follicular phase (OR 1.11, 95% Confidence Interval (CI) 1.03 – 1.20; p=0.006) and lower in the luteal phase (OR 0.90, 95% CI 0·83 – 0.98; P=0.027) of mutation carriers compared to non-carriers. Median luteal phase progesterone and estradiol levels were respectively 121% (p<0.001) and 33% (p=0.007) higher in mutant compared to controls. These results were not due to differential oral contraceptive use.

We were also recently part of a collaborative effort suggesting that progestogens may increase breast cancer risk by inducing RANKL (receptor activator of NF-κB ligand) expression. In addition, work in progress clearly demonstrates that estrogen-regulated genes show aberrant epigenetic alterations in the fimbrial Fallopian Tube (the area close to the ovary from which the majority of ovarian cancer in *BRCA* mutation carriers develops) but not in the proximal Fallopian Tube (the area close to the uterus which is not at increased risk of becoming malignant). We also have preliminary data to show that compromised *BRCA* function leads to over-activation of a long-non-coding RNA called HOTAIR which blocks stem cell differentiation.

The present proposal includes the recruitment of women with Lynch Syndrome. Lynch Syndrome (LS) is a heritable syndrome characterised by a spectrum of cancers, which include endometrial cancer, colorectal cancer, ovarian cancer, kidney cancer, ureteric cancer, gastric cancer, small bowel cancer, and hepatobiliary cancer. It is caused by an alteration in one of the DNA mismatch repair genes: MLH1, MSH2, MSH6, or PMS2 (Lynch and de la Chapelle, 2004; Broaddus et al, 2004).

Overall these findings strongly support the hypothesis that *BRCA* mutation carriers undergo systemic changes during the menstrual cycle, which lead to specific epigenetic alterations that trigger alterations in stem cell differentiation and contribute to breast and ovarian cancer development. To elucidate these mechanisms it is crucial in order to (1) develop tools that allow the detection women with a inherited mutation in the absence of a family history, and (2) to develop less invasive yet effective tools to prevent breast and ovarian cancers in *BRCA* and Lynch Syndrome mutation carriers.

To achieve this we aim to develop a large cohort of women with a known mutation in the *BRCA* or Lynch genes and their mutation-free female family members, as well as women who undergo surgical procedures for non-cancer reasons.

We intend to use various media to invite women to participate and contribute to the research and are setting up research clinics that aim to achieve the following:

1. Explaining the core purpose of our research and explanation of the intended collections and seeking written consent for specific projects as detailed below.
2. Epidemiological questionnaire to establish their personal medical and gynaecological history.
3. Collection of samples (saliva, cervical and buccal swabs, endometrial, urine samples as well as venous/menstrual blood samples) and agreement to be able to take surplus tissue in case the patient will undergo surgery. For practicality, we will provide women with home-collection kits where possible, so menstrual blood and urine can be collected in privacy and stored safely.

Although these samples will be tested for genetic and epigenetic risk factors, our role will be research-focused and not diagnostic in any way. No genetic information will be communicated to the volunteers participating in the proposed study.

6. Study Design / Methodology

This is a prospective case-control study. The main approach will be to actively recruit women with *BRCA* mutation as well as Lynch Syndrome, with appropriate controls. Where possible we would select controls with proven negative mutation status. However, we will also include general population controls. In such cases, the will be able to indicate on the consent form whether they would like to be informed of any potentially positive genetic test outcome. Because the genetic techniques employed in this study are experimental, they are not considered diagnostic and cannot be used to reliably rule out the presence of a genetic mutation. However, if a research participant opts to be informed of a potential presence of a genetic mutation, they will be offered post-test counselling and follow-up with the Familial Cancer Centre team at UCLH, who in turn can refer for standard genetic testing.

7. Recruitment/Inclusion criteria

We intend to recruit 800 mutation carriers and 1500 individuals with no known gene mutation, as well as 1000 women with current breast, ovarian, endometrial or cervical cancer.

1. Woman aged >18 years of age
2. Documented *BRCA1/BRCA2* gene mutation (cases) or documented absence of a *BRCA* mutation, as well as unknown mutation status (general population controls) and women with current cancer as detailed above (breast, ovarian and endometrial).
3. Women with Lynch Syndrome (MLH1, MSH2, MSH6 and/or PMS2 mutation carriers) registered with the familial gynaecological cancer clinic or identified as Lynch Syndrome due to their family history or mutation status in other clinics (e.g., genetics clinic, gynaecology clinic, medical oncology clinic, colorectal cancer clinic, general practitioner clinic).

8. Exclusion criteria

The following will be excluded from the study:

1. Women who have undergone previous hysterectomy
2. Women who had recent non-gynaecological cancer (any cancer) treatment (within 2 years of recruitment)
3. Women who are pregnant or who are menstruating at the time of recruitment.
4. Women who have had a cervical smear in the last 12 weeks prior to sample donation.

9. Sources of Recruitment

Known *BRCA* mutation carriers and *BRCA* wildtype carrying family members:

1. Women who attend the Familial Cancer Clinic (FCC), Elizabeth Garrett Anderson Wing, UCLH, as well as Gynaecological Cancer Clinics at UCL Partners and Royal London Hospital.

2. Women who attend any FCCs/Clinical Genetics Services in the London Cancer catchment area (including clinics to discuss prophylactic surgery – i.e., bilateral mastectomy and/or salpingo-ophorectomy and/or hysterectomy).

3. Women identified as *BRCA* mutation carriers due to their family history or mutation status in other clinics (e.g., gynaecology clinics, medical oncology clinics, genetic services, general practitioner clinics, etc.).

4. Women who are already enrolled in United Kingdom Familial Ovarian Cancer Screening Study (UKFOCSS): one of the largest clinical trials in the world for women with an inherited risk for breast and ovarian cancer. To date, around 30% of the study population have undergone clinically initiated testing (either prior or subsequent to recruitment) for *BRCA1* and *BRCA2* mutations. Invitations to participate will be sent to women with documented *BRCA1* mutations, focusing first on those who have agreed to participate in research studies in the past, for example by giving permission to use their serum or blood.

5. Individuals at high risk of familial gynaecological cancer already registered on the database of UCLH, UCL Partners, and other NHS Hospital Trusts, as well as women undergoing treatment for cancer at collaborating sites.

6. Women who want to contribute to research and have not been registered in 1-3 but have heard about or been invited (e.g., via adverts or through social or conventional media) to participate in our research. In particular, we would like to invite by letter women registered with the largest UK patient interest group for individuals with a *BRCA* mutation, the 'BRCA Umbrella' forum.

Controls from the general population:
1. Who undergo surgery for non-cancer reasons and who have been genetically tested for inherited cancer risk, or are attending hospital for non-oncological reasons (principally general gynaecological patients).

2. Women who want to contribute to research and have heard (e.g., via adverts or through social or conventional media) about our research, and have undergone genetic testing and found not to carry the relevant genetic mutations.

10. Recruitment

We aim to recruit study participants by letter and electronic invitations. Volunteers will be invited to participate from the Familial Cancer Clinic (FCC), Elizabeth Garrett Anderson Wing, UCLH, Gynaecological Cancer Clinics at UCL Partners and Royal London Hospital, as well as from charities with which we have established working relations, as well as through other channels.

All potential research participants will be invited to a short meeting where UCL personnel will explain the rationale and background of the study, give detailed instruction on how to collect and store biological samples, and provide them with kits for saliva sample collection and urine testing where applicable. Volunteers' travel expenses will be reimbursed. The UCL personnel will also go over the text of the informed consent during that meeting and address any question about this consent. Following appropriate time for question and reflection, study subjects will then be

invited to sign the consent form. They will also be asked to complete an epidemiological questionnaire about their medical and reproductive history after signing informed consent.

Eligible individuals consenting to participate will be recruited and allocated a unique volunteer reference number (VRN). Information collected will include patient details e.g. name, address, NHS number, GP details, demographic information and summary of family history of breast, ovarian and other cancers and any epidemiological data relevant to the project.

All participants will be provided with a detailed participant information sheet to help them make an informed decision regarding participating in the study. It covers issues pertaining to the implications of participating in the study, the advantages and disadvantages, sources of independent information and contact details for the study team. Participation will be completely voluntary and free and under no circumstances impact any clinical care received. The participant information sheet is attached to this application.

It is recognised that some potentially eligible research participants will decline any participation. This will in no way affect their routine clinical care.

Individuals who are found to be *BRCA* / Lynch Syndrome mutation positive following testing will be provided their test result at a face to face counselling session. Post-test counselling will include pedigree analysis, risk assessment and individually targeted risk-reduction options. Volunteers will be further referred (via their GP) to a high-risk regional genetics clinic.

11. Routine Research Protocol

Women who have agreed to participate in our study will be given an appointment in a dedicated Research Clinic.

The appointment will be structured in 5 parts, as explained below.

1. Detailed explanation of the projects, including the rationale, details of study interventions, expectation for follow-up and clear demarcation of the limits of the study.
2. Seeking consent to participate (for providing epidemiological data and samples – to be collected now (see (4) and during surgery if applicable – and for agreeing to follow up over the set time frame (25 years).
3. Epidemiological questionnaire will be distributed and completed as part of the session. Ample time will be given to answer questions and feelings that may arise. The questionnaire (attached) will cover reproductive history, personal and familial history of any cancer, exposure to exogenous hormones, menstrual as well as general medical history.
4. Collection of up to 40 mL blood, buccal swabs, cervical swabs (endo- and ectocervix), in addition to other samples as required (listed below). It will be made clear that the smear samples will be provided for research only and would not alter the need for each participant (where relevant) to continue adhering to the national cervical cancer screening programme.

5. BRCA mutation carriers (selected subgroup) will also be invited to fill in a psychological questionnaire to explore the psychological impact of living with a risk-causing gene mutation.
6. All cases who provide tissue samples will also have Clinical Data Forms filled in to detail what histological type, Grade, Stage and other clinico-pathological features.
7. Explanation of follow-up and expected outcomes, as well as opportunity to clarify any aspect of the appointment.

Following comprehensive counselling and information, women who participate in the study will be offered the opportunity to donate blood and urine sample, cervical and buccal swabs, as well as tissue surplus to diagnostic requirements as part of any surgery. Patients will be streamed into different groups, so as to ensure that they do not feel that they have to donate all of the above types of samples.

Group 1
Number of participants: 1000 cases, 1500 controls
Biosamples collected: Blood, buccal, endo- and ectocervical swabs, as well as tissue samples collected at time of surgery (if applicable).
Following relevant information and consent, research participants will be able to donate these biosamples in the privacy of a dedicated research clinic. Only appropriately trained staff will be able to collect the samples. The method of obtaining each sample varies according to type of sample. Blood tests, urine and buccal swabs would be collected in a private area of a clinic or surgical pre-assessment. Cervical cells may be obtained in a private setting in a clinic by an appropriately trained health care professional, or during general anaesthesia if the patient is undergoing surgery.

Group 2
Number of patients: 150 cases, 150 controls
Biosamples collected: Endometrial washings
Following relevant information and consent, research participants will be able to donate these biosamples at the same time as they undergo gynaecological surgical procedures. All participants will have undergone general anaesthesia as part of their surgical procedure. Only appropriately trained staff will be able to collect the washings. The lavage procedure is carried out in the following manner. Lavage fluid is slowly flushed into the uterine cavity and proximal tubes. Simultaneously, the plunger of the empty syringe is gently pulled out, sucking the fluid from the uterine cavity and proximal tubes. While one tube slowly empties, the other slowly fills up. In the majority of cases, the exact same amount of fluid that is flushed into the uterus is retrieved from the cavity, making it very unlikely that any fluid is lost through the tubes into the peritoneal cavity.

Group 3
Number of patients: 80 cases (BRCA1 mutation carriers), 80 controls (BRCA1 mutation negative - both aged 18-45)
Biosamples collected: Saliva and menstrual blood samples
Following relevant information and consent, research participants will be able to donate these biosamples using collection kits in the privacy of their home. Daily saliva samples as well as menstrual blood samples for the duration of one menstrual period,

will be collected by the participant and posted to the laboratory in pre-formatted envelopes. Urine ovulation test to be taken on Day 14 and 15 of cycle, and blood samples fro AMH, cytokine levels as well as functional immune tests taken on Day 4, Day 15 and Day 4 (of the next menstrual cycle). Fecal samples taken on Day 4 of two consecutive menstrual cycles to assess the gut microbiome.

Samples will be subjected to a range of genetic, epigenetic, protein and hormone-based, transcriptome/microbiome-based tests, and other biological analyses to identify signature markers involved in early cancer development.

Follow-up would be carried out by questionnaires in letter form at regular intervals during the 25 year follow-up period. Access to Hospital Episode Statistics (HES) will be sought as part of the consent form.

13. Sample Collection and Storage

All biological samples will be collected by trained staff. All samples will be labelled and anonymised at point of recruitment, as detailed in the SOP. Samples will be sent to the co-ordinating centre laboratory at the UCL Cancer Centre for processing and storage.

Samples would be stored under the custodianship of the UCL Biobank (REC Approved, 10/H1306/42), as part of our on-going collection (NC09.13 - Prospective collection and analysis of tissue specific biological samples for translational research of women specific cancer).

In the laboratory samples will be spun, aliquoted, databased and stored in liquid-nitrogen/ -80°C as appropriate. Blood cells will be separated into specific subsets of cells (using MACS technology). No personal data are stored within the Labvantage system; samples are identified with a unique sample ID linked to the participant through a separate database. The system is one that we have used for a considerable time and we have robust safety routines to ensure all samples are stored safely and anonymously.

Luteinizing hormone determinations (of time of ovulation) will be obtained from urine samples; the study subjects will be instructed on using the Clearblue Fertility Monitor test for ovulation (www.swissprecisiondiagnostics. com) in the middle of their cycle to document the luteinizing hormone surge indicative of impending ovulation. Within UCL Clinical Research Facility (CRF) we will collect and isolate menstrual stem cells using collection technology and expertise provided by Cryo-Cell International Inc.

Samples taken will be stored under the custodianship of University College London. These stored samples will be used for future research studies. Volunteers who decline to provide samples for storage/ future research can still participate in the initial cycle of experiments.

14. Withdrawal of Volunteers

Volunteers are free to withdraw from the study at any time, through personal choice or without giving any reason for doing so and without this affecting their clinical care.

15. Sample Size and Power

The initial project sample size for Group 1 is projected to be 800 cases (*BRCA* mutation positive/Lynch Syndrome) and 800 age-matched controls. These figures comprise a larger number who donate blood, cervical cells, urine and saliva/buccal samples.

Justification for the proposed sample size of the discovery set is given based on the outcome of previous prospective EWAS studies performed by us, as well as independent epigenome-wide association study (EWAS) power calculations (Rakyan et al, 2011), both converging on similar estimates.

The power calculations are based on statistical methodology (Pawitan et al., 2005) designed for quantitative data types such as gene expression (but also applicable to DNA methylation), and was applied to two data sets (Anjum et al., 2014):

(1) The UKCTOCS serum DNA methylation set, consisting of 134 prospective breast cancer cases and 148 matched controls)

(2) A set of white blood cell DNA from 30 *BRCA1* mutation carriers and 30 age-matched *BRCA1* wild type controls

Power estimation in this setting depends on several parameters, including the percentage of truly differentially methylated sites, the average effect size of these sites, the proportion of cases with differentially methylated sites and sample size. Based on previous data, it is reasonable to assume that at least 1% of measured CpGs (spatially uncorrelated CpG elements) are differentially methylated between cases and controls at an average effect size value, which we have estimated by averaging the effect sizes of the top 1% of risk CpGs from our previous UKCTOCS study (Anjum et al., 2014). Assuming further that on average 50% of cases show alterations at these specific sites, we can see that for a significance threshold of 1e-4, sensitivity values are close to 80%, while FDR is <0.05. For the scenario where we declare the top 1% CpGs as significant, the FNR equals the FDR (Pawitan et al., 2005), and we can see that only when

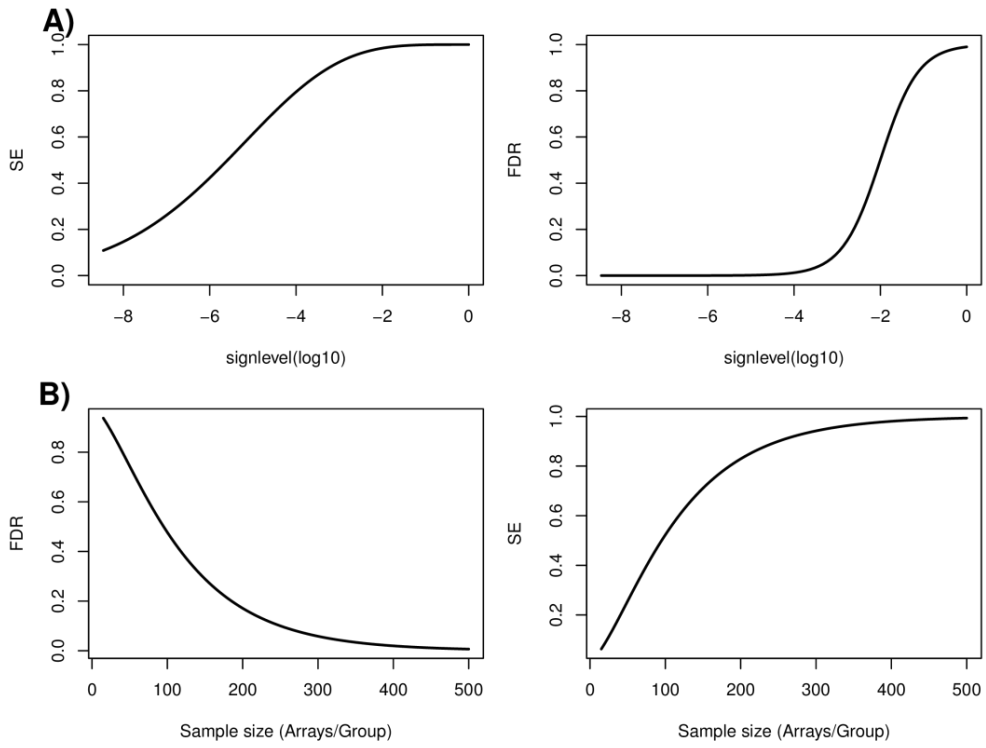

Figure 14: Power calculations based on prospective data from the UKCTOCS cohort. A) Sensitivity (SE) and FDR against significance threshold for scenario described in text. B) Plots of FDR and Sensitivity (SE) against sample size (#samples per phenotype) for scenario where we declare the top 1% of CpGs to be significant.

we have 300-400 sample in each phenotype that we obtain an FDR < 0.05-0.1 and a sensitivity above 80%. Typically, we would require operating characteristics of FDR < 0.05-0.1 and sensitivity values of 80% or higher to ensure construction of highly accurate and clinically applicable prediction algorithms as it has been done before for clinical tools based on -omics data (Van't Veer et al., 2002).

Application of the same power analysis do data set (2) – *BRCA1* mutation carriers vs controls - would reveal that high sensitivity (>80%) and low FDR (<0.05) could be achieved with approximately 100 cases and 100 controls.

16. Health Service Research Issues

Preliminary economic evaluation will be undertaken using the data collected. There will be a direct analysis of the screening strategy that will be based on the cost per case detected. There is also a treatment follow-up arising from the surgical intervention associated with the screening strategy. Economic evaluation will calculate the incremental cost per successfully treated case, with additional modelling based on the treatment risk reduction converted into changes in life expectancy. Modelling will also be used to estimate the resource impact as based on standard practice, which would reflect the implementation of existing screening and surgical risk-reduction programmes. Such resource issues will also be explored in the extrapolation of study results over a longer time frame to include lifetime benefits.

17. Study Organisation / Management

The co-ordinating team will be based at the Women's Cancer Translational Research Centre, Institute for Women's Health, University College London, UK.

The staff at the coordinating centre will include the PI, co-PIs, study investigators, study co-ordinator, clinical fellow, clinical nurse specialist, recruitment assistants, database manager, statistician as well as a team of clerical, laboratory and technical staff. The study co-ordinator will be responsible for the day-to-day management issues.

The co-ordinating centre will be responsible for-

- Confirming eligibility of participants and registration with the study.
- Overall co-ordination and management of the study.
- Liaison with collaborators and regional genetic clinics
- Answering queries about the study
- Sample collection and transport
- Storage of samples for any future analysis
- Mailing of questionnaires
- Collection and data-basing of data
- Data review for the Study Management Group

18. Data Management

Data management for the trial will be carried out using our customised Labvantage database developed for this purpose. Data capture from the questionnaires may be outsourced to a data capture company. Data forms sent for this purpose will be coded.

19. Study Management Group

The management group will consist of the PI, co-PIs, trial investigators, selected lead researchers, and key research staff to review progress on a regular basis. This group will be responsible for day-to-day management of the study, monitoring and supervising progress, adherence to protocol and safety of participants.

UCL Joint Research Office Declaration

"University College London holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, if this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participants of the clinical study. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS trust or otherwise."

Every participant will be given the following information as part of the Patient Information Sheet:

"If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated by members of staff you may have experienced due to your participation in the research, National Health Service or UCL complaints mechanisms are available to you. Please ask your research doctor if you would like more information on this. In the unlikely event that you are harmed by taking part in this study, compensation may be available. If you suspect that the harm is the result of the Sponsor's (University College London) or the hospital's negligence then you may be able to claim compensation. After discussing with your research doctor, please make the claim in writing to Professor Martin Widschwendter, who is the Chief Investigator for the research and is based at the Department of Women's Cancer, UCL Institute for Women's Health, 74 Huntley Street, London WC1E 6AU. The Chief Investigator will then pass the claim to the Sponsor's Insurers, via the Sponsor's office. You may have to bear the costs of the legal action initially, and you should consult a lawyer about this."

Group Members

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Prof Usha Menon (co-PI)
Dr Adam Rosenthal (co-PI)
Dr Lucy Side
Dr. Ranjit Manchanda
Prof Mo Keshtgar
Dr Rebecca Roylance
Dr Andrew Teschendorff
Dr Dan Reisel

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