NORMAN BEISCHER MEDICAL RESEARCH FOUNDATION

Year 2 Report

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Project Title:	The CODEC Study (Circulating tumOur Dna in Endometrial Cancer)
Grant:	$61,000
Initial year of funding:	2018

Provide a short summary of your project, activity or area of study:

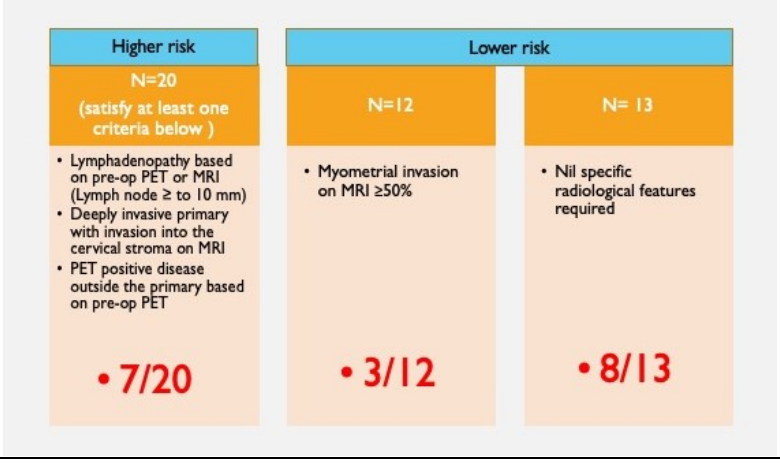
The CODEC study is a pilot proof of concept study assessing the utility of circulating tumour DNA (ctDNA) as a prognostic biomarker in endometrial cancer. Tissue samples are collected from patients' primary tumours to facilitate genomic profiling which will be matched to the ctDNA in the blood. ctDNA will then be measured at 16 different time points across the patient's disease course. This project has the potential to answer a number of important research questions and provide feasibility to take this technology forward into future clinical trials with the hope of improving the outcome for women with this disease.

How to select patients with endometrial cancer for adjuvant chemotherapy remains a dilemma that plagues oncologists even today, particularly in those with early stage disease. We hope that this study will show that ctDNA is prognostic and can be used to guide selection of patients for adjuvant therapy; specifically, in helping to define those patients at lower risk that may be spared chemotherapy and those at higher risk that may benefit most from intensive treatment. This study also has a number of additional exploratory end points including the investigation of the prognostic capacity of ctDNA compared to imaging techniques including PET and MRI and the possibility that ctDNA may be able to molecularly sub-classify tumours.

Outline your progress to date:

The first patient was recruited to CODEC in June 2019 and since this time, recruitment has been faster than anticipated. In 8 months, we have recruited 26 patients across the two sites (15 from Epworth and 11 from the Royal Women's Hospital [RWH]). Of the 26 patients recruited 18 have fulfilled all eligibility (18/45 40% of target population Figure 1).

Figure 1-Overview of the recruitment arms



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Of the 11 patients recruited from the RWH, one did not get to surgery and one had her tumour grade downgraded. Another two patients declined all further medical treatment following surgery including follow up, and thus were withdrawn from the study. The seven remaining patients fulfilled all eligibility and remain enrolled. From the 15 patients recruited at Epworth, 11 remain eligible and enrolled. Three of 15 had their tumour downgraded and one was found have a primary cervix cancer rather than an endometrial. In this case we were subsequently able to facilitate this patient's enrolment in another study, the Stafford Fox Rare Cancer Program with the hope of allowing her access to genomic testing that may be useful for her future care.
The patients recruited to date having been of varying histologic type and stage (Figure 2) and have been recruited to all of three arms of the study (Figure 1).

Of the 18 participant we have tumour genomic results are available on nine participants of whom seven have genomic alterations that may be potentially actionable in future clinical trials. All of the nine cases sequenced to date have mutations that can be tracked in the ctDNA.

Figure 2-Overview of the recruitment to date

Histological subtype	Stage	Adjuvant therapy	Germline change	Molecular subtype	Genomic change with potential therapeutic impact	Target for ctDNA
Carcinosarcoma	1A	N	N	TP53m	*PIK3R1*	*TP53, ARID1A,APC,KRAS,PIK3R1,PTEN*
Clear cell	IVB	Chemo	*MUTYH*	TP53WT	N	*SMAD4, TAF11, PIK3CA*
Grade 3 EAC	1A	Obs	*MSH6*	MMRd	High TMB, MMRd, Signature 15, PIK3CA	*MSH*6 (somatic), *PTEN, KRAS*
Serous	IVB	Chemo	N	TP53m	*MYC* amplification	*TP53, PPP2R1A,GRIN2A*
Carcinosarcoma	1A	N	N	TP53 WT	*PIK3CA, FGFR2*	*FGFR2,PIK3CA, ARID1A,PTEN*
Mixed grade 2 EAC/serous	1A	Brachy	N	POLE	POLE, hypermutated phenotype, High TMB, Signature 10, Signature 14	POLE, MSH6,PIK3CA, PTEN, APC
Carcinosarcoma	1A	Brachy	N	TP53WT	N	*MDM2, LZTR1,NF1*
Carcinosarcoma	IVB	Chemo	N	TP53m	*NF1, PIK3CA, AKT1,MTOR*	*TP53, PIK3CA, AKT1, MTOR, RB1, NF1*

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Is the project proceeding in accordance with the original submission? If not outline any obstacles you have encountered:

As mentioned in our previous report, there were a number of delays at the beginning of this study due to finalising contracts between Epworth and various parties including the Peter MacCallum Cancer Centre for utilisation of PET, Molecular Pathology and phlebotomy services, The Centre of Biostatics and Clinical Trials (BaCT) and The Royal Women's Hospital.

We had envisaged beginning recruitment at The Royal Women's Hospital at the beginning of February 2019, however due to updates with the ethics and further revision of the research agreements, the study did not officially begin recruitment until June 2019. In addition, it took a number of months to recruit the first patient at Epworth. However, once the gynae-oncology team were familiar with the study processes, recruitment has been rapid.

Other comments:

We are very pleased with the study's progress and hope to begin analysis of the ctDNA and complete recruitment in the first half of 2021.

Comment from Dr Nicole Brooks, Research Manager, Epworth Molecular Oncology & Cancer Immunology Unit:
I am confident that Rachel Delahunty has made excellent progress in recruiting to her endometrial ctDNA study. She has captured a range of histological subtypes and we are looking forward to analysing the data to see what molecular profiles these samples will have. Based on these sample types our team at Peter Mac Laboratories will be able to confirm which genomic panel is best to use. We are very satisfied with the progress of this project.