Promising new model for the molecular classification of endometrial cancers

Drs Jessica McAlpine and **Aline Talhouk** are both scientists working in the Gynaecological Cancer Research Program (OVCARE) at the University of British Columbia and BC Cancer Agency in Canada. Talhouk is a biostatistician who has worked on many projects on endometrial and ovarian cancers, while McAlpine is a gynaecological oncologist who divides her time between surgical and clinical duties and scientific research. They are currently collaborating on a clinically applicable molecular assay in endometrial cancers that identifies risk of recurrence and death as well as opportunities for targeted treatment.

Endometrial carcinoma (EC) is the most common gynaecological cancer in the developed world and the sixth most common cancer in women overall worldwide. The number of new cases and deaths associated with EC are increasing. Most women with early stage disease (I and II) have favourable outcomes, and 75-90% live more than five years after diagnosis. However, those who present with advanced stage disease or aggressive subtypes have a very poor prognosis, and are typically unresponsive to chemotherapy.

DIAGNOSIS IS INCONSISTENT

Endometrial cancers are assigned a grade, a histologic subtype and ultimately a stage (after surgery) by pathologists. However, even expert pathologists find it difficult to agree upon grade and histotype in many cases. Treatment (type of surgery, and need for additional chemotherapy or radiation) is decided based on the pathologist's opinion. This makes risk determination fallible and means that the same woman may receive a different diagnosis from different doctors or healthcare centres. Consequently, women may be overtreated, e.g., unnecessary chemotherapy or other treatments, or may be undertreated, missing an opportunity for cure.

Additionally, determination of the stage of disease is only possible following surgery (removal of the uterus, ovaries, fallopian tubes, and often other procedures). For women who wish to preserve their fertility, having earlier information about the risk of their cancer having spread or the likelihood that their cancer will come back would be helpful. 14% of women with endometrial carcinoma are under the age of 50 and these women may wish to avoid or delay definitive surgical intervention. This team has developed a method by which the molecular character of a tumour can be determined on a simple sample of the endometrium (obtained for diagnosis) and does not require hysterectomy (removal of the womb).

All women would benefit from more personalised information about their cancer to enable better decision making on treatments needed and even tailoring treatment specifically to their individual tumour. In addition, the molecular tests performed in ProMisE can identify women who might have a hereditary (passed down within the family) condition that might put them at risk of developing other cancers. If a family syndrome is found, the patient and her relatives can undertake increased screening and/or risk-reducing steps that might save their lives.

A PROMISING MODEL

The most comprehensive molecular study of EC to date is The Cancer Genome Atlas (TCGA). This project identified four prognostic groups within EC cases which shared molecular similarities but may be classified differently by traditional risk stratification approaches. Inspired by these findings, McAlpine and Talhouk set out to investigate whether these groupings could be identified using less costly and technically complex molecular analysis techniques than the TCGA project had at their disposal.

The team has paid strict attention to the Institute of Medicine's guidelines for developing 'omics' based tests (the collective name given to molecular technologies such as genomics and proteomics) which 'aim to ensure that progress in omics test development is grounded in sound scientific practice and is reproducible, resulting not only in improved health care but also in continued public trust'. Starting with sixteen possible models on a small 'discovery' cohort, the team eventually narrowed down their methods and sequence options to a single model for testing in a larger 'confirmation' cohort. This model was named as the **Pro**active **M**olecular R**is**k Classifier for **E**ndometrial Cancer (ProMisE for short), and validated in a large cohort of over 500 participants with help from collaborators at the University of Tübingen in Germany.

The ProMisE model represents a cost-effective assay that can be implemented in a clinical setting to improve the categorisation and risk stratification of endometrial cancer”

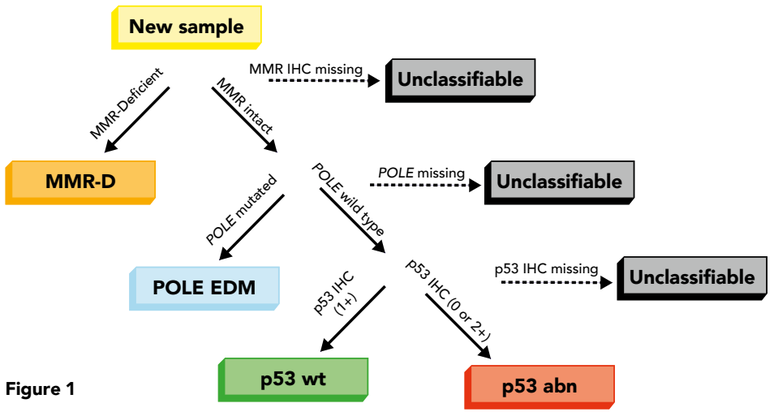

Figure 1

BRANCHING OUT

These investigations resulted in the development of a 'molecular decision tree' (Figure 1) which guides the assessment of the tumour sample and categorises it into one of the four groups or 'unclassified'. Specific methodologies include Immunohistochemistry (IHC) for identification of the '**MMR-D**' (mismatch repair protein deficient) subgroup; digital PCR to identify *POLE* exonuclease domain mutations ('***POLE* EDM**'); and IHC for '**p53wt**' (wild-type) and '**p53abn**' (null/mutated).

These markers are mostly distinct from those identified in the complex methods used by TCGA, so it was necessary to ensure that they were as relevant to the outcomes. This team showed in over 450 ECs assessed that their model was highly prognostic, using components that are less subjective and more reproducible than what have historically been relied on.

Further analysis by the team demonstrated that, 'women within each molecular subgroup have clinicopathological characteristics that have consistently been shown to be typical of that group. For example, the p53abn subgroup usually encompasses the highest proportion of high-grade, advanced stage, non-endometrioid histotypes.' This group consequently has the worst outcomes, with the *POLE*-EDM group faring best and the two remaining groups occupying distinct areas between these two curves in all three measures of outcome: overall survival; disease-specific survival; and progression-free survival (Figure 2). In addition, this team has tested their model on diagnostic biopsies and shown high concordance with final hysterectomy samples suggesting any tissue sample can be used (even the earliest obtained) to guide management of women with EC.

Endometrial carcinoma is the most common gynaecological cancer in the developed world and the sixth most common cancer overall in women worldwide

POISED FOR FURTHER DEVELOPMENT

The final validation cohort studies have just been completed and show promising results. In publications this year, McAlpine and Talhouk show the following: that ProMisE can consistently categorise endometrial carcinomas into four distinct prognostic subgroups; this can be achieved on diagnostic biopsy specimens with high level of agreement with final hysterectomy specimens; and that the prognostic information is at least as good, if not better, at determining outcomes than the currently used European Society of Medical Oncology (ESMO) risk stratification system.

The next step is to test ProMisE in the clinics, and determine how this tool can best be used. Clinical trials are planned where ProMisE is applied to diagnostic specimens and to stratify women into different cohorts, determining surgical management and additional therapies (if any). Patient outcomes, satisfaction/quality of life, and health economic impact will all be measured.

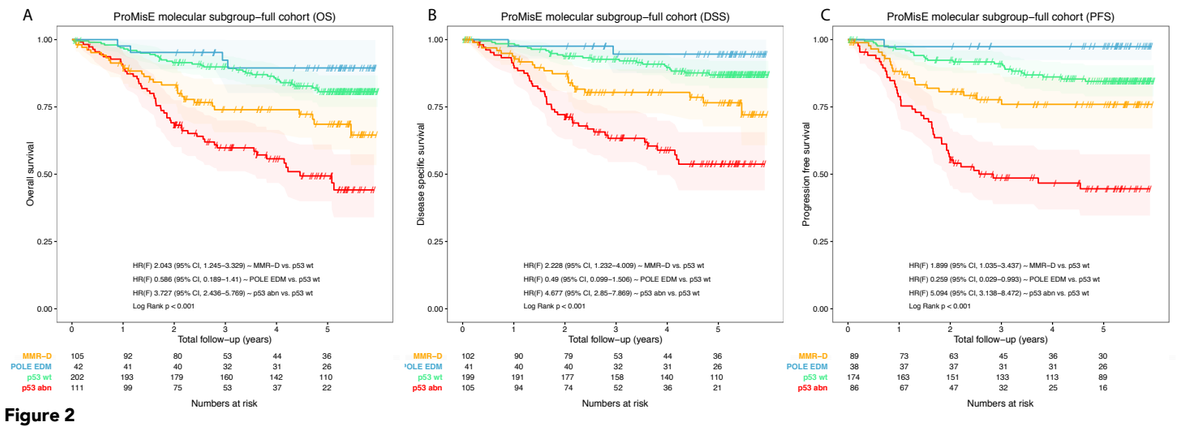

Figure 2

Q&A

Why do you think endometrial cancers have previously been under-researched?
I think that because historically most women do well and survive this disease, it gained less attention. However, from a raw numbers perspective it is an incredibly common disease that should raise the alarm (~10,000 new cases in the UK, ~60,000 new cases in the US last year). We have an urgent need to do better for the 20–25% of all ECs diagnosed that have bad outcomes, and to try and spare the women who have very favourable outcomes from unnecessary treatments and worrisome visits.

What attracted you to this area of research?
Seeing the challenges that pathologists face every day and that managing oncologists (for example, me, as a surgeon) subsequently face in determining which surgery or treatment(s) is best. I have worked in five different cancer centres and seen at least five different strategies in management. Even in our own centre there is often disagreement as to what is 'best'.

How has your previous work informed your current research?
Working on ovarian cancers with a 'subtype-specific' approach has certainly changed clinical management and research. The same rationale and desire for a paradigm shift was clearly needed in endometrial cancer.

Do you think ProMisE could soon replace other methods of cancer diagnosis, such as ESMO?
I don't think any component currently used in risk stratification will be completely abandoned, although some factors may hold less importance. Specific parameters, like tumour grade, patient age, or ESMO risk group may be added to ProMisE and provide greater prognostic strength. In the coming months, working with 1000 cases tested thus far, we will be testing which factors are the most important to move forward with. As our German collaborator has said (and taken from a German proverb) we don't want to throw the baby out with the bathwater!

What do you think is the most significant benefit of your model?
Consistent reproducible prognostic categorisation of endometrial cancers so that treatment effects can be studied and optimised within the same categories.

THE BENEFITS OF PROMISE

The clearest benefit of the ProMisE model is consistent categorisation of endometrial cancers so that 'apples' can be studied with 'apples' and the best treatment for a category of tumours can be determined. Therapy can be more tailored to the individual, meaning that there could be fewer negative side-effects associated with over-treatment and less missed opportunities of under-treatment. This will minimise the disruption to a person's life as well as the potential complications from treatment. For those who are diagnosed before they reach menopause, this may offer a chance to preserve their fertility by avoiding or delaying complete surgical staging if it is unnecessary. Of course, this also implies an economic saving for healthcare services if fewer costly treatments are required.

There are further specific benefits to McAlpine and Talhouks' model, including identifying women who may have a hereditary cancer syndrome (Lynch Syndrome) that puts them at higher risk of developing other cancers. ProMisE can provide empowering information about the behaviour/biology of a tumour, informing women how likely it is that their cancer will come back or how likely they are to die from this disease. Targeted therapy, specific to ProMisE subgroup, can be applied, offering a step towards precision medicine. Overall, the model represents a cost-effective assay that can be implemented in a clinical setting to improve the categorisation and risk stratification of endometrial cancer. Drs Talhouk and McAlpine believe this represents a turning point to improving outcomes for the thousands of women who develop this disease every year.

Detail

RESEARCH OBJECTIVES

Together, Drs McAlpine and Talhouk have developed this molecular classifier stemming from an international study, the Cancer Genome Atlas (TCGA). McAlpine and Talhouk made the molecular tests simpler and at lower cost so that testing could be performed in any cancer centre.

FUNDING

Canadian Institutes for Health Research; BC Cancer Foundation; Vancouver General Hospital & UBC Foundation; VCHRI

COLLABORATORS

C Blake Gilks, David G Huntsman, Melissa McConechy, and Samuel Leung have been critical to the success of this project. We are grateful for local and international collaborators including Dianne Miller; Janice Kwon; Stefan Kommoss; Frieder Kommoss; Lien Hoang; Anthony Karnezis; Cheng Han Lee; Niki Boyd; Rob Soslow; Martin Kobel and our fantastic lab team of Amy Lum, Winnie Yang, and Janine Senz.

BIO

Dr Aline Talhouk is a biostatistician working with BC's Gynecological Cancer Research (OVCARE) team. She completed her PhD in Statistics at UBC in 2013 with a focus on computational statistics and machine learning, and was the recipient of an Alexander Graham Bell Graduate Scholarship.

Dr Jessica McAlpine is from Vancouver but received her medical training in the US, returning in 2006 to join the OVCARE team. She is an Associate Professor at UBC and Director of the OVCARE Tumor Bank. She is the recipient of the 2012 CIHR New Investigator Award and the 2016 BC Cancer Foundation Clinical Investigator Award.

CONTACT

Dr Jessica N McAlpine, MD
OvCaRe Research Program
675 West 10th Avenue
Vancouver BC V5Z 1L3 CANADA

E: info@ovcare.ca
T: +1 604 675-8211
W: http://www.ovcare.ca