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Precision medicine in endometrial cancer

These are exciting times to be a clinician or researcher in gynecologic cancers. Over the last decade we have witnessed how a subtype-specific approach to ovarian cancers has dramatically changed management, including what surgery is performed, and which or if any adjuvant treatment is needed. We are poised to make the same transformation in endometrial carcinomas (EC). EC is the most common gynecologic cancer in the developed world and the 4th most common cancer in women overall. With increasing obesity, and declining hysterectomy rates the disease burden is predicted to increase even further and become second only to breast cancer within 20 years [1,2]. Recognizing the challenges and inadequacies of classifying endometrial cancers based on histomorphological features we have been motivated to interrogate molecular features in order to better categorize tumors and identify biologically and behaviourally- 'like' tumours. The Cancer Genome Atlas Project (TCGA) was instrumental in this transition, identifying four prognostic molecular subtypes of ECs [3].

The key molecular features used to identify the four molecular subtypes have been meticulously explored and characterized by both the Vancouver/ProMisE and Leiden/TransPORTEC teams over the past 5 years [4–8]. Their molecular classification systems were inspired by TCGA but use clinically relevant, practical methodologies achievable on standard formalin-fixed paraffin-embedded (FFPE) specimens. ProMisE (**Pro**active **M**olecular R**is**k classifier for **E**ndometrial Carcinomas) was developed according to the strict Institute of Medicine Guidelines for the development of 'omics-based biomarkers, successfully completing the development [5], confirmation [7] and validation [8] phases before clinical application. The four molecular subtypes identified by ProMisE include mismatch repair deficient ('MMRd') as determined by MMR immunohistochemistry (analogous to TCGA MSI-H subtype), 'POLE' characterized by the presence of a pathogenic mutation in the exonuclease domain of DNA polymerase epsilon and analogous to TCGA *POLE* ultramutated phenotype, p53 abnormal ('p53abn') and 'p53wt' based on immunostaining for p53 and corresponding to Copy number-high (CN-H) TCGA subtype and Copy number-low (CN-L)/No Specific Mutational Profile or 'NSMP' TCGA and Leiden subtypes respectively.

Molecular classification has subsequently been used to stratify past and ongoing clinical trials [9] in an effort to interpret treatment efficacy within molecularly similar tumors. The prognostic value of molecular classification has been established across diverse patient cohorts [4–8], stratifying ECs into groups with significantly different progression free, disease-specific, and overall survival. More recently, the predictive value of molecular subtype assignment has been suggested, with improved response rates to radiotherapy, conventional and targeted systemic therapies observed within specific molecular subtypes [10,11]. Stratification is further supported by the FDA-approval of anti-PD-1/PD-L1 therapies for MSI-H/MMRd EC in 2017. International collaborative investigations indicate that favorable outcomes observed in *POLE* mutated ECs may be independent of treatment [12]. In addition, preclinical data demonstrates low sensitivity of POLE ECs to both radiation and carboplatin/taxol regimens [13]. The predictive implications of these data are that most *POLE* mutated ECs may be cured by surgery alone and women could be spared adjuvant therapies and their associated toxicities. Such examples of molecular classification-driven changes to treatment algorithms will impact both patient quality of life and health care resources.

In this month's Gynecologic Oncology, Prendergast at al, characterize an aggressive cohort of recurrent endometrial cancers through genomic profiling [14]. Testing standard FFPE tumor samples from recurrent (80%) or primary (20%) EC and using a large hybrid-capture next generation sequencing (NGS) panel to genomically characterize the tumors, they were able to assign molecular subtype for all cases. As expected, the largest proportion of these recurrent cases were within the poor prognosis p53abn/CN-H subtype followed by intermediate risk p53wt/CN-L and MMRd/MSI-H. Their series highlights the need for better treatments for p53abn EC as current approaches to treatment were insufficient to prevent recurrence. Their results also confirm prior observations that, with the exception of serous carcinomas that are almost always p53abn/CN-H subtype, molecular subtypes did not closely correlate with histotype, grade, or stage.

Their team sought to identify opportunities for targeted therapy through profiling and were able to direct treatment in a subset of these women, documenting stable disease in 37% and objective responses in 25%. The authors confirmed anti-tumor activity of immune blockade in these heavily pretreated ECs, with treatment selection based on MSI/MMRd status or increased tumor mutational burden. Perhaps most impressive was the 69 month duration of treatment response to tyrosine kinase inhibitor therapy in the woman with the only POLE mutated EC identified in this cohort. Genomic profiling also revealed possible mechanisms of resistance to anti-PD-1 therapies and hormonal regimens. The authors conclude that genomic profiling in recurrent ECs might be justified as part of routine clinical care, identifying opportunities for matched therapies.

This publication prompts important discussion about the role, associated costs and timing of molecular profiling in ECs. The authors describe testing patients with recurrent EC, where the realistic goal was to identify effective palliative therapy. Could the described benefit of testing recurrent EC samples (TCGA classification and biomarker identification for matched therapies) be realized by upfront testing of primary ECs e.g., molecular classification at time of first diagnosis? Might this model provide better value for women with EC through early identification of women who should be referred to a hereditary cancer program, providing prognostic information, and directing therapy, with the goal

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of decreasing cancer mortality? The largest category of targeted therapy in the Prendergast series was immune blockade which can be stratified through immunostaining for mismatch repair proteins. Current clinically approved small, focussed, next generation NGS panels (as opposed to the larger hybrid capture panels) that include *POLE* hotspots can also assess P13K/PTEN pathways, HER2 status and other clinically relevant genomic alterations cited in this series. For early stage disease, such information might be acted on immediately or could be available should the patient experience disease recurrence. Molecular classification makes studying treatment efficacy within biologically- 'like' ECs feasible. Primary tumour testing would enable us to explore the role of specific therapies earlier in the disease course (vs. after multiple lines of conventional chemotherapy), with the ultimate aim of treatment for cure in the adjuvant setting, rather than palliation after multiple recurrences. The monumental impact witnessed by administration of PARPi as first line therapy in high grade serous ovarian cancer as compared to the recurrent setting, also seen with traztuzumab for breast carcinoma, should inspire efforts to move targeted therapies to as early a point as possible in the disease course. NRG-UC1805 seeks to address this question, comparing radiation alone to radiation followed by pembrolizumab in early stage (I/II) MMRd endometrial carcinomas.

Further support for early molecular classification can also be found in this issue of Gynecologic Oncology where Abdulfatah et al demonstrate high concordance of molecular subtype assignment between diagnostic endometrial biopsy and final hysterectomy specimen post-staging in cases of EC (n=50) and atypical hyperplasia/EIN (n=10) [15]. Importantly, the authors observed that concordance of molecular subtype (kappa ~ 0.9) far exceeded the level of agreement for grade and histotype assignment (kappa~ 0.5). The authors emphasized the prognostic value of ProMisE and the opportunity for 'early personalized patient management' from time of first diagnosis. What patient or clinician would not want to know the biology/behaviour of their tumor as early as possible, enabling improved decision making on the timing/urgency and aggressiveness of surgical staging or need (if any) for adjuvant therapy? Earlier information might also direct which women could be cared for in the community as opposed to a tertiary cancer center.

Abdulfatah's paper follows publications in 2014 by Stelloo et al [16] and 2016 by Talhouk et al [17] comparing biopsy vs. hysterectomy specimens and the value of molecular vs. pathological features. Subsequently, in 2018 Kommoss et al reported on 156 diagnostic biopsy/curetting's compared with hysterectomies citing overall accuracy of 0.92 and kappa statistic of 0.99 (95% CI 0.79-0.94) [8]. Importantly, all three series and the current manuscript have observed a very low likelihood that the most aggressive subtype of ECs; p53abn, would be missed. Reasons for disagreement between molecular subtype assignment in biopsy and hysterectomy have included cases of dedifferentiated tumors where both low grade and high grade components co-exist in the final hysterectomy specimen but only one of which may be sampled on biopsy [17]. Lack of agreement for detection of *POLE* mutations in biopsy/curetting specimens and hysterectomy in the Abdulfatah series (2 cases where the biopsy was negative and hysterectomy positive) may be attributed to technical factors as Sanger sequencing is less sensitive for detection of mutations (~ 15 % allelic frequency) compared to NGS platforms, which can detect mutant alleles of genes of interest at much lower frequencies of 1-2%. Like MMR loss, acquisition of *POLE* mutations is an early event in EC carcinogenesis [18], detected in both early ECs and atypical hyperplasia/EIN thus we do not suspect a change in *POLE* status over the usually short time between diagnostic biopsy and staging, but think it more likely to reflect the need for a sensitive assay for use in endometrial biopsy samples, where tumor cellularity may be relatively low.

In summary, it is fantastic to see endometrial cancer having its day in the spotlight, with two articles supporting molecular classification as a step towards personalized medicine for this common disease. It has long been clear that we need to move beyond pathological categorization of ECs to reproducible molecular profiling. We propose, however, that upfront molecular classification; composed of MMR and p53 IHC and targeted NGS panel testing of primary EC, performed on the biopsy specimen and achievable for approximately $500 might be a better investment of health care resources than isolated, higher cost testing of select recurrent ECs. Upfront molecular classification provides both prognostic and predictive information for patients and clinicians; identifying one of the most common (and FDA-approved) targeted therapeutic opportunities for women with MMRd ECs as well as prompting consideration of withholding adjuvant therapy in *POLE* mutated ECs. We have a tremendous opportunity to study the effectiveness of molecular classification-driven treatment algorithms as compared to the current highly variable standard of care. We believe that it will be more impactful to determine clinical outcomes and treatment efficacy using EC molecular subtypes to guide management early in disease course rather undertaking more comprehensive characterization in a small number of recurrent ECs, diverse with respect to histotype, stage, grade, prior treatment and molecular features, after the window of opportunity to treat with intent to cure has closed.

Author contribution

Dr. McAlpine was the primary writer with content suggestion, direction, and edits from both authors.

Conflict of Interest

The authors have no conflicts of interest to declare.

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