Molecular Profiling of Endometrial Cancer From TCGA to Clinical Practice

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ABSTRACT

Molecular classification provides an objective, reproducible framework for categorization of endometrial cancers (ECs), informing prognosis and selection of therapy. Currently, the uptake of molecular classification, integration in to EC management algorithms, and enrollment in molecular subtype-specific clinical trials lags behind what it could be. Access to molecular testing is not uniform, and subsequent management (surgical, adjuvant therapy) is unacceptably variable. We are in the midst of a critical landscape change in this disease site, with increasing emphasis on the integration of molecular features in EC care that can potentially improve standard of care globally. This article summarizes the rationale for molecular classification of ECs, strategies for implementation in low and high resource settings, and actionable opportunities based on this information.

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Endometrial cancer (EC) is the most common gynecologic malignancy in North America, with incidence and mortality rates increasing globally.[1] The majority of patients with EC have low-grade and early-stage disease with favorable outcomes, often cured by surgery alone. However, approximately 20% of patients may have advanced stage disease or be at high risk of recurrence and death from disease. Identifying these individuals in order to inform them of their prognosis, perform the right surgery, and administer the best adjuvant therapies to improve their outcomes remains the greatest challenge in this disease site. Historical risk stratification systems are based on histomorphologic features, such as grade and histotype, both of which have been shown to have poor reproducibility even among expert gynecologic pathologists.[2–4] Imprecise categorization of ECs has resulted in marked variation in clinical practice[5,6] and difficulty interpreting clinical trials in which biologically diverse tumors have been grouped together for study. These challenges underscore the need for a consistent, objective EC classification system.

Discovery of the 4 Molecular Subtypes by The Cancer Genome Atlas

In 2013, The Cancer Genome Atlas (TCGA) reported on a comprehensive molecular multiplatform assessment of 307 endometrioid and 66 serous ECs.[7] Using a combination of whole genome or exome sequencing, microsatellite instability (MSI) assays, and copy number analysis, ECs were grouped into 4 distinct molecular subtypes based on genomic architecture. A novel ultramutated subtype was identified (~10% of the endometrioid cohort), with somatic mutations in the exonuclease domain of DNA polymerase epsilon (*POLE*), a gene involved in DNA lead strand replication and proofreading/DNA repair. These ECs have a high proportion of C>A but low C>G transversions and markedly high mutational frequency (>100 mutations per megabase [mut/Mb]). Clinical outcomes within the *POLE* ("ultramutated") subset were highly favorable (0 progression-free survival events within the TCGA cohort; in subsequent series, >96% disease-specific 5-year survival)[8–15] and clearly distinguishable from the other 3 molecular subtypes. A second molecular subtype reported by the TCGA shows MSI,

with low copy number variation but high mutational frequency (>10 mutations/Mb; "hypermutated") and intermediate outcomes. The third subtype, also with intermediate outcomes, was characterized by a low number of somatic copy number alterations ("copy number low"), and comparatively low mutational burden, frequently in the *PI3K/Akt* and *wnt/CTNNB1* signaling pathways. These ECs were mostly endometrioid histology and exhibited high levels of estrogen and progesterone receptor (ER/PR) expression. The fourth and final molecular subtype in TCGA was characterized by high somatic copy number alterations, low mutation rate, nearly ubiquitous *TP53* mutations, and molecular similarities to high-grade serous ovarian cancer and basal-like breast cancer. Patients with "copy number high" EC had aggressive disease and poor outcomes (<50% 5-year survival). This discovery of the 4 prognostic EC subtypes by the TCGA was transformational; however, methods used were high-cost, and not easily translated into clinical practice.

Development of Pragmatic Classifiers

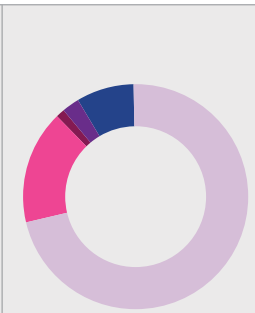
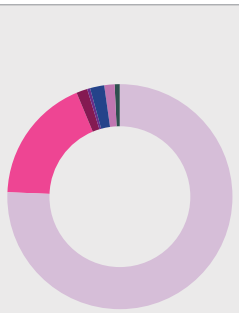
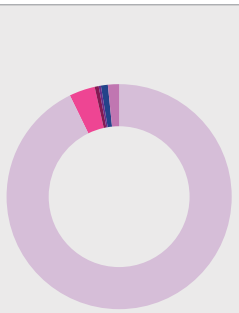
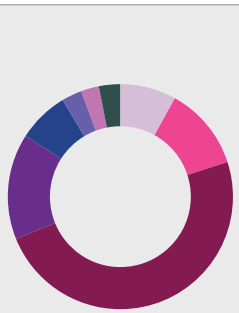
Following the TCGA discovery, 2 research groups independently developed a molecular classification tool that used lower cost, clinically applicable methods to identify 4 EC molecular subtypes (*POLE*mut, MMRd, NSMP, and p53abn; Table 1).[8–10,12,13] ProMisE (Proactive Molecular risk classifier for Endometrial cancer) and the TransPORTEC initiative combine focused next-generation sequencing (NGS) for detection of pathogenic *POLE* mutations and immunohistochemistry (IHC) to assess mismatch repair (MMR) proteins and p53 status. Although the 4 molecular subtypes identified by these pragmatic tools were defined differently compared with TCGA, the clinical outcomes/survival curves mirrored TCGA, with rare to no disease-specific progression or death events within *POLE*mut (approximately 8%–10% of all ECs), the worst outcomes within p53abn ECs (~15% of all ECs, but responsible for >50% of EC mortality), and intermediate outcomes in patients with MMRd tumors (approximately 25%–27% of ECs) and NSMP ECs ("no specific molecular profile," defined by an absence of these key molecular features and encompassing ~50% of population-based series).

This pragmatic classifier is feasible on formalin-fixed paraffin-embedded (FFPE) tumor specimens and has been shown to be highly reproducible,[8–10,12,13] with interlaboratory concordance[16] and high concordance between biopsy and hysterectomy samples.[10,17–19] It has also been shown to have strong prognostic significance across unselected populations,[10] clinical trial populations,[20] and even age-[21] and histotype-restricted series.[22–24] More recent data support the predictive implications of molecular subtype assignment. Molecular subanalysis of clinical trial data and a large retrospective series have demonstrated improved outcomes in patients with p53abn ECs treated with platinum-based chemotherapy compared with radiation alone in patients with ESMO-defined high-risk EC. In contrast, no apparent benefit of chemotherapy was observed in these series for patients with high-risk MMRd ECs.[20,25] Individual patient data meta-analysis of all published and available international reports on *POLE*mut ECs showed that patients with confirmed pathogenic *POLE* mutations have almost no recurrence or disease-specific death events, even when their tumors appear to have unfavorable clinicopathologic or molecular characteristics, and adjuvant treatment was not associated with outcomes.[14] Excellent survival outcomes in *POLE*mut ECs were also confirmed in a more recent meta-analysis,[26] and in a 2022 publication from a Danish database in which patients with high-grade *POLE*mut ECs who received no adjuvant treatment encountered no recurrence events.[15] Taken together, these data support de-escalation of therapy in this molecular subtype. Further support for the predictive role of molecular subtype to stratify targeted therapy opportunities are discussed later in this review.

Incorporation of Molecular Classification Into Clinical Practice and Clinical Trials

In 2020, the 5th edition of the *WHO Classification of Tumours: Female Genital Tumours* was published, recommending integration of molecular parameters into standard EC pathology reporting.[27] NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) recommend ancillary studies to test for *POLE* mutations, MMR/MSI, and p53 status to complement morphologic assessment of histologic tumor type.[28] The European Society of Gynaecological Oncology (ESGO), European Society for Radiotherapy and Oncology (ESTRO), and European Society of Pathology (ESP) have jointly published guidelines that integrate molecular subtype into risk group assignment and direct adjuvant therapy recommendations for each risk group.[29] This has significant impact, reassigning all stage I–II *POLE*mut ECs as low risk with the option of no additional therapy and designating all p53abn ECs with any myometrial invasion (MI) as high risk (intermediate risk if no MI). These new guidelines have been applied to retrospective series that had undergone molecular classification, revealing 33% of patients with *POLE*mut ECs had received more treatment than would currently be recommended (ie, possibly overtreated), and conversely, 42% of patients with p53abn ECs were potentially undertreated and would have been directed to additional adjuvant therapy under current guidelines.[5] Molecular classification would direct an overall change to EC management in 10% to 11% of all patients.[5,30] It is impossible to know if this change in management would have improved survival of patients in these retrospective series, but it inarguably has implications for cost and toxicity.

Table 1. Endometrial Cancer Molecular Subtypes

	***POLE*mut**	**MMRd**	**NSMP**	**p53abn**
TCGA category	*POLE* "ultramutated"	MSI "hypermutated"	Copy number low	Copy number high
Associated clinical features	Lower BMI Frequent stage I Earlier onset	Lynch syndrome–associated	Higher BMI High proportion estrogen-driven	Lower BMI Older Frequent advanced stage
Prognosis	Excellent (>96% 5-year survival)	Intermediate	Intermediate to excellent subset of ER-negative with poor outcomes	Poor (~50% 5-year survival)
Histopathologic features	High TILs; frequently high grade; LVI; unfavorable pathologic and molecular features; "ambiguous morphology"	High TILs; frequent LVI; mucinous differentiation and MELF-pattern invasion	Mostly low grade; frequent squamous differentiation; low TILs	Majority high grade; high nuclear atypia
Histologic distribution Endometrioid, low grade Endometrioid, high grade Serous Carcinosarcoma Mixed Clear cell Dedifferentiated/ Undifferentiated Other				
Molecular features	High TMB (>100 mut/Mb) Very low SCNAs MSS	TMB (10–100 mut/Mb) Low SCNAs MSI	Low TMB (<10 mut/Mb) Low SCNAs MSS and absence of *POLE* or *TP53* mutation	Low TMB High SCNAs MSS
Diagnostic test	NGS/Sanger/RT-PCR for *POLE* EDM or hotspot pathogenic[a] mutations	IHC: MSH2, MSH6, PMS2, MLH1 MSI assay NGS for MMR genes	Diagnosis after exclusion of other features (eg, *POLE*-wt, MMRp, p53/*TP53*-wt) Recommend ER status substratification	IHC: p53 (null or overexpression); NGS for *TP53*
Treatment considerations	Observation/De-escalation	Immune checkpoint blockade Radiation	Endocrine therapy if ER-positive De-escalation in selected stage I	Chemotherapy Substratification to target HRD, HER2 overexpression, immune-angiogenesis, or *CCNE1* pathways

Abbreviations: BMI, body mass index; EDM, exonuclease domain mutation; ER, estrogen receptor; HRD, homologous recombination deficiency; IHC, immunohistochemistry; LVI, lymphovascular invasion; MELF, microcytic, elongated, and fragmented; MMRd, mismatch repair deficient; MMRp, mismatch repair proficient; MSI, microsatellite instability; MSS, microsatellite stable; mut/Mb, mutations/megabase; NGS, next-generation sequencing; NSMP, no specific molecular profile; SCNA, somatic copy number alteration; TCGA, The Cancer Genome Atlas; TIL, tumor-infiltrating lymphocyte; TMB, tumor mutational burden; wt, wild-type.
[a]P286R, V411L, S297F, A456P, S459F, P436R, F367S, L421I, M295R, M444K, D368Y.

Molecularly classification has also enabled clinical trials to assess treatment efficacy within biologically similar tumors. There is an increasing number of molecular subtype–specific clinical trials assessing (1) the safety of de-escalation of adjuvant treatment in *POLE*mut EC (PORTEC-4a [ClinicalTrials.gov identifier: NCT03469674]; TAPER/EN.10/RAINBO-POLEmut-BLUE [NCT05640999 and NCT05255653]); (2) immune checkpoint blockade (ICB) in MMRd tumors (NRG-GY018 [NCT03914612], NRG-GY020 [NCT04214067], and RAINBO/MMRd-GREEN [NCT05255653]); and (3) PARP inhibitor and other targeted therapies + chemotherapy in p53abn ECs (CAN-STAMP [NCT04159155], RAINBO/p53abn-RED [NCT05255653], GOG-86P,[31] and GOG-3053/KEYNOTE-B21 [NCT04634877]), to name a few. Enrollment to these trials is strongly encouraged, not only to determine optimal treatment strategies within molecular subtype but also to demonstrate feasibility of molecular testing for routine clinical care.

Strategies and Challenges for Implementation

Despite the abundance of data on the value of molecular classification in EC in recent years, and the WHO endorsement of integration of molecular features into pathologic

reporting, clinical uptake has been highly variable. This is mainly attributable to the cost and limited access to clinically approved assays for *POLE* mutation testing. Perhaps less easy to explain is the number of centers still not routinely performing comparably low-cost (approximately $50–$75/IHC marker), easy-to-interpret IHC testing for MMR proteins and p53. Different cancer centers have adopted different strategies for molecular testing, with some centers routinely testing all newly diagnosed ECs for all molecular components, and some advocating for routine IHC assessment of MMR and p53 status for all ECs, but testing *POLE* by NGS only when adjuvant treatment would be altered by knowing *POLE* status. Talhouk et al[32] recently validated a "selective" ProMisE testing protocol in which p53 and MMR IHC were performed on all ECs with omission of *POLE* sequencing in very-low-risk EC. These very-low-risk cases were defined as cases fulfilling all of the following: grade 1/2, MMR-proficient, p53 wild-type, endometrioid histology, stage IA, no lymphovascular invasion (LVI). Universal MMR and p53 IHC testing, and foregoing *POLE* testing in patients with very-low-risk ECs in which this has no therapeutic impact avoided *POLE* testing in 38% of this population-based series.[32] This restricted/selective *POLE* testing strategy has been adopted in the United Kingdom (April 2022)[33] and in British Columbia, Canada (May 2022), where proposals justifying costs and resources for *POLE* testing were required before funding for patient testing was approved. Notably, there is active research toward development of low-cost *POLE* assays[34] that may help centers with limited resources embark on routine *POLE* testing.

Perhaps the second greatest barrier to implementation is knowledge translation; there is a need to increase clinician awareness of the already existing extensive data on prognostic information that molecular subtype provides, promote published clinical guidelines that integrate molecular subtype into risk stratification and treatment recommendations (ESGO/ESTRO/ESP[29] and NCCN[28]), and endorse molecular subtype-specific clinical trials. It will be critical in the next 3 to 5 years that the impact made by molecular classification, both in research and clinical care, is actively communicated to patients and clinicians, and that steps are taken to ensure equal access to molecular testing and precision management.

Actionable Opportunities for Molecularly Defined ECs

*POLE*mut Endometrial Cancer

As outlined earlier, patients with pathogenic[35] *POLE*mut EC have excellent clinical outcomes,[8–15,20] even when they have tumors demonstrating adverse clinicopathologic (eg, deep invasion, high grade, extensive LVI) or molecular (eg, L1CAM overexpression, *CTNNB1* mutations) features. It is critical to differentiate between a defined list of 11 *POLE* exonuclease domain mutations (EDMs) that have been both genomically and clinically interrogated to confirm pathogenicity from a constellation of nonpathogenic *POLE* mutations that can arise even within the EDM, which have inferior clinical outcomes and should not be considered for deescalation.[14] For patients with *POLE* pathogenic mutations, favorable outcomes do not appear to be associated with receiving adjuvant treatment.[14,15] In the rare patients with *POLE*mut ECs who do develop a disease recurrence, salvage rates were observed to be high, and sustained, with long-term survival from 5 to 14 years postrecurrence reported.[14] These data support participation in clinical trials assessing the safety of de-escalated therapy in *POLE*mut ECs (as listed earlier), and have led to change in treatment guidelines by ESGO/ESTRO/ESP wherein all early-stage (I–II) *POLE*mut ECs are now designated low risk and may be offered no additional therapy.[29]

MMRd Endometrial Cancer

MMR status has implications for Lynch syndrome (LS) testing[28,29] as well as FDA-approved ICB therapy for patients with advanced or recurrent MMRd ECs. ICB therapy has also been administered for early-stage EC in the context of clinical trials (as listed earlier). Recent data from small series have highlighted the possible diversity within MMRd tumors, with worse outcomes observed in patients with MLH1 loss compared with LS-associated MMRd EC,[36] and lower response to ICB.[37] We await maturation of data from larger clinical trials to affirm whether there are statistically significant differences in response to ICB within MMRd tumors.[38] These data, as well as the observed differences in immune profiles within MMRd tumors,[39,40] highlight the need for biomarker stratification within this molecular subtype.

p53abn Endometrial Cancer

The 2020 ESGO/ESTRO/ESP EC guidelines recommend all p53abn ECs with MI be considered high risk; and be treated with chemotherapy ± radiation.[29] Although the importance of chemotherapy is generally accepted in advanced-stage p53abn ECs, there is perhaps less certainty in some centers regarding treatment of early-stage p53abn ECs. In the PORTEC-3 trial, 37 of 93 (40%) high-risk (according to ESMO 2016 criteria) patients with p53abn EC were stage I, including 23 with stage IA EC.[20] A large retrospective series in which treatments were administered according to institutional protocols at the time had included 228 patients with stage I p53abn (175 stage IA, 53 stage IB) within the high-risk (ESMO 2016 criteria) cohort, again showing improved outcomes in patients who had received chemotherapy with radiation compared with radiotherapy alone.[25] A recent Danish series in high-grade ECs that were

fully staged with lymphadenectomy demonstrated that even true stage I p53abn ECs had poor survival outcomes, and suggested that the unfavorable prognosis of p53abn EC appeared to be independent of stage.[15]

Patients with stage IA p53abn EC without MI have been categorized by ESGO/ESTRO/ESP 2020 guidelines as intermediate risk and might be offered surgery alone (no adjuvant therapy) or vault brachytherapy (± chemotherapy).[29] A recent assessment of a retrospective cohort of 80 patients with stage IA p53abn ECs without MI who did not receive adjuvant therapy showed rates of recurrence of approximately 17%,[41] raising the question of whether these patients should also have received additional treatments. It is important to remember that approximately 5% of low-grade (grade 1 or 2) endometrioid ECs are p53abn.[42–44] These patients have been observed to be older and thinner, with worse clinical outcomes.[42] Recent assessment of low-grade p53abn ECs within the PORTEC-1/-2 trials and retrospective cohorts demonstrated that these patients had a high rate of disease recurrence, even within stage I disease (29.5% 5-year recurrence rate in stage I disease),[44] again far exceeding usual thresholds for treatment and supporting application of the 2020 ESGO/ESTRO/ESP guidelines to consider these patients high risk and offer treatment[29] and/or consider enrollment in clinical trials.

Beyond the supported role for chemotherapy in p53abn ECs,[20,25] p53 status may also be considered as a stratification feature for antiangiogenic agents[31] + chemotherapy, ICB + chemotherapy, or combinations, with appreciation that the subset of patients with MMRp tumors most likely to benefit from combined pembrolizumab/lenvatinib may be those with p53abn ECs.[45] Subsets of p53abn high-risk tumors are recognized to have targetable features, including 20% to 25% with HER2 overexpression,[46] 20% to 40% with homologous recombination deficiencies,[47–49] and 30% to 50% with *CCNE1* amplification.[7,48] Molecular subtype–specific trials (examples listed previously) with substratification within p53abn ECs may offer an opportunity to finally improve outcomes for patients with these aggressive tumors.

NSMP Endometrial Cancer

Perhaps the greatest attention is needed in prognostic and predictive refinement within NSMP tumors, encompassing 50% of ECs. NSMP ECs are enriched in estrogen-driven low-grade indolent tumors but also capture aggressive histotypes (eg, clear cell carcinoma, dedifferentiated carcinoma, gastric-type mucinous carcinoma, mesonephric-like carcinoma),[27] for which optimal management is unclear. Current guidelines that integrate molecular subtype are not prescriptive and do not alter risk group assignment within NSMP ECs,[29] relying mostly on pathologic features. In contrast to *POLE*mut ECs, research focusing specifically on NSMP ECs has shown that additional clinicopathologic and molecular features are strongly associated with outcomes and may aid in prognostic and predictive substratification of this molecular subtype.[50]

Surgical Staging

Molecular subtype has recently been demonstrated to be a strong predictor of lymph node metastases (LNM) in EC, with the highest rate of LNM observed in p53abn ECs at approximately 45%.[51] Other metastatic sites of disease, such as the omentum, have been shown to be involved in 18% to 24% of p53abn ECs, supporting omental sampling and pathologic assessment, which may impact adjuvant treatment decisions.[51,52] Given that molecular classification can be accurately performed on endometrial biopsies,[10,17–19] often with better antigen preservation and high tumor volume/cellularity compared with hysterectomy specimens, molecular classification at diagnosis could, in the future, be used to direct surgical procedures.

Although lymph node dissection is not believed to have a therapeutic benefit in EC,[53,54] upstaging in both MMRd and NSMP tumors is impactful, changing risk group assignment in the ESGO/ESTRO/ESP guidelines[29] and having the potential to improve outcomes through conventional (eg, radiation for MMRd ECs) or targeted therapies (eg, ICB for advanced-stage MMRd tumors). The impact of removing clinically occult nodes and upstaging in p53abn ECs is less clear given that current ESGO/ESTRO/ESP guidelines[29] classify all p53abn ECs with any MI as high risk and recommend adjuvant chemotherapy (± radiation) for all patients, regardless of stage, grade, and histotype. However, in centers where treatment administered for stage I p53abn ECs is different from that administered for stage III p53abn ECs, this nodal information may still be needed. Unquestionably more research is needed in this area to direct surgical care and balance the morbidity and costs of this intervention.

For patients found to have pathogenic *POLE* mutations, data from an international metanalysis show a 5.7% rate of LNM (of 294 pathogenic *POLE* mutations), with 10.2% of cases having not undergone any nodal assessment. A recent institutional series in which full pelvic and paraortic lymph node dissection was performed in all patients suggested that the rate of LNM may be higher in patients with *POLE*mut ECs (14.2%)—a rate as high as MMRd ECs (14.9%) and higher than NSMP ECs (11%).[51] However, this series included just 21 *POLE*mut ECs (2 patients with macrometastases, 1 with micrometastases, no isolated tumor cells/ITCs), and thus may be less representative. Most importantly, even with this observed higher rate of LNM there were no recurrence events, consistent with the excellent outcomes observed across all *POLE*mut studies. These data again support consideration of de-escalated therapy, but also question the value of knowing nodal status in these molecularly

defined ECs. As more data are collected, optimal surgical procedures to perform in patients with EC and the impact of knowing nodal status (including ultrastaging findings such as ITCs) will be able to be assessed in the framework of molecular classification. Future algorithms may direct surgery as well as adjuvant treatments according to molecular subtype.

Summary

Molecular classification provides consistent categorization of ECs, enabling the identification of "biologically like" cancers for research discovery, subtype-specific clinical management, and clinical trials. Molecular subtyping provides both prognostic and predictive information for patients and clinicians and a framework in which further substratification can be undertaken. Performing molecular classification on endometrial biopsy/curettage enables informed care from first diagnosis. Ensuring access to molecular testing across all centers, and strong prescriptive guidelines on how to use this information for both practitioners and patients can help reduce the current high variation in pathologic and clinical practice and support a pathway to more equitable care. Stratification of EC treatment based on the molecular classification in clinical guidelines will help drive implementation globally and improve standard of care in this disease.

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