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Primum non nocere: Are we ready for POLE testing in endometrial cancer?

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Substantial interest in the clinical application of DNA polymerase epsilon gene (*POLE*) mutation testing has been generated since the initial identification of the *POLE* molecular class of endometrial cancer made by The Cancer Genome Atlas (TCGA) in 2013 (1). TCGA reported that tumors classified as *POLE* have a high somatic mutation burden (thus referred to as ultramutated) and that women whose tumors were ultramutated had impressive progression-free survival. No recurrences were seen among the seventeen TCGA patients with *POLE* tumors. Since the time of the initial TCGA publication, additional reports on the prognostic significance of *POLE* mutations in endometrial cancer have appeared (2–6). With mounting evidence that women with *POLE*-mutated tumors have improved recurrence-free survival, gynecologic oncologists have questioned whether their patients with *POLE*-mutated tumors may not need adjuvant therapies, and could thus be spared the toxicities associated with radiation or systemic therapies. It is logical to assume that if patients with *POLE*-mutated tumors do not recur, then they may not benefit from adjuvant treatments. Unfortunately, exciting discoveries can easily be over-emphasized by the commercial genetics testing industry and without extensive vetting of data and physician education, commercial marketing of new tests might compromise individualized cancer care decisions. To date, studies have not provided a clear answer as to the clinical utility of *POLE* testing because of conflicting reports on survival benefit, uncertain biologic role for some *POLE* mutations, uncertainty as to how *POLE* mutations interact with other molecular features, and most importantly that molecular class:treatment interactions have not been adequately addressed.

Personalized medicine and targeted therapy have captured the attention of both clinicians and patients. The number of potential biomarkers for personalized cancer care has increased dramatically with advances in profiling technologies and informatics. How best to use *POLE* mutation testing for the management of endometrial cancer patients, however, presents us with a clinical dilemma: If adjuvant therapy is otherwise indicated, can we spare patients

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with *POLE*-mutated tumors the morbidity associated with chemo- and/or radiation therapy? The decision to withhold treatment, as might be the case for patients with a *POLE*-mutated tumor, should be made when there is high confidence that such action will not compromise patient outcomes. The precept “first, do no harm” demands that physicians weigh potential benefits and risks. Concern of recurrence has in many instances driven our medical decisions leading to periods of disease overtreatment. However, in an era of molecular medicine a reduction in adjuvant therapy toxicity has been observed in both breast and colorectal cancers. Hormone receptor status in breast cancer has shifted cytotoxic therapy to hormonal treatments while in colorectal cancer management the appreciation that microsatellite unstable tumors do not benefit from 5-FU based chemotherapy has allowed for reduction of chemotherapy in a group that was not deriving survival benefit.

Risk stratification in endometrial cancer is not a new concept; routine management decisions are based on several clinicopathologic features that together guide use of adjuvant therapy. Clinicians can provide appropriate counseling based on evidence supported by randomized clinical trials. So why would we approach molecular risk stratification differently, without the guidance of prospective validation? The published retrospective studies have demonstrated that some endometrial cancer patients with *POLE*-mutated tumors do recur (be it a low frequency), unlike the 17 patients in the initial TCGA study. Overall, the data suggest that outcomes are better for *POLE*-mutated cases (1, 5, 6), but some studies failed to demonstrate a significant difference in outcomes (2, 3). The published series have helped refine the prognostic significance of select *POLE* mutations but did not address *POLE*'s role as a predictive marker.

The favorable outcomes for women with *POLE*-mutated tumors have been attributed to the high number of mutations in tumors, expression of mutant proteins (neoantigens), and increased patient immune responses (7, 8). It is yet to be determined if the *POLE*-mutated tumor status leads to an improved response to adjuvant therapy or if the tumor's enhanced immunogenicity allows for the patient's immune system to manage the cancer without additional therapies. The data currently available have not provided insights into the outcomes for women with *POLE*-mutated tumors that did not receive adjuvant therapies. Does *POLE* mutation status matter in multivariable analyses that include adjuvant therapy? Without an answer to this question we may run the risk of “undertreating” women whose cancers harbor a *POLE*-mutated tumor and cede the improved outcomes observed in the molecular class.

In light of the uncertainty as to what if any adjuvant treatment interactions exist for *POLE*-mutated tumors, can we make decisions about which patients would potentially be candidates for *POLE* testing? Several of the series examining *POLE* have included non-endometrioid cases as well both early and advanced stage cases. At present withholding therapy for a non-endometrioid or advanced stage patient could be seen as irresponsible without significant data suggesting that we are not compromising outcomes. The most practical application of *POLE* testing could be for early stage patients with endometrioid histology tumors, notably grade 3. The complexity and uncertainty as to what the best approach to adjuvant therapy decision making in this group (early stage, grade 3 patients) is highlighted by the NCCN guidelines (9) where therapeutic options range from observation

to pelvic radiation +/- vaginal brachytherapy +/- chemotherapy. Patients with grade 3 endometrioid tumors would benefit from further refinement in algorithms used in adjuvant therapy decision. *POLE* mutation is associated with higher grade tumors, making *POLE* testing even more likely to be relevant in grade 3 cases. The prognostic significance of *POLE* mutation testing for grade 3 endometrioid tumors has been explored in several series (3, 5, 6, 10) with the weight of evidence pointing to improved outcomes for women with *POLE*-mutated grade 3 tumors. Although a pooled multivariate analysis of five studies involving grade 3 endometrioid tumors by McConechy and colleagues (6) demonstrated improved progression-free survival HR=0.32 (0.11–0.97), overall and disease-specific survival were not statistically significant. What if any interactions exist between *POLE* mutation status and adjuvant treatment is not fully understood. At this time, any assumption that withholding therapy would not adversely affect outcomes for women with grade 3 tumors is based on limited retrospective data. This, however, does not mean *POLE* testing will not be an important step in personalized medicine for endometrial cancer patients. Instead, it seems likely that *POLE* analysis will have its greatest impact as part of more comprehensive tumor profiling studies.

A binary classification of *POLE*-mutated or *POLE* non-mutated would be a user friendly approach for prognostication, but seems naïve in light of the currently available data. TCGA demonstrated 14% of MSI tumors also carried a *POLE* mutation. It was noted that *POLE* mutations may lead to somatic mutations in mismatch repair genes (2). Relying on *POLE* status alone may not adequately predict tumor biology and could lead to misguided counseling and/or management. Another important question that is yet to be addressed is whether all *POLE* mutations have similar effects. TCGA and the subsequent studies all identified recurrent P286R and V411L “hotspot” mutations which represent about two-thirds of *POLE* mutations. These hotspot mutations along with several additional mutations are located within the exonuclease domain of *POLE* (amino acids 268–471). The missense mutations associated with the ultramutator phenotype disrupt exonuclease activity that is critical to high fidelity DNA replication. While all the hotspot mutations were seen within the *POLE* molecular class in TCGA, several non-hotspot mutations were also observed in the *POLE* subgroup as well as the MSI subgroup. A *POLE* mutation was even identified in the high risk “serous-like” subgroup. The impact that non-hotspot mutations and multiple molecular features have on tumor biology remains unanswered.

The provocative outcomes data presented by TCGA as well as others have generated significant interest in the *POLE* molecular class. With the paucity of available data and understanding of the role of *POLE* in endometrial cancer management, providers and patients may have false hopes for “cure” without additional therapy. Molecular classification of endometrial cancer is on the horizon. The increasingly reliable and cost-effective techniques promise to be part of our practice in the near future. The advancing technology and expanding literature will allow for further subclassification of endometrial and other cancers. Molecular risk prediction models will no doubt become part of practice and change our management algorithms. The goal of all this, of course, is to improve and personalize cancer care.

TCGA provided a framework for molecular classification of endometrial cancers and translation of TCGA findings to patient care is ongoing. The *POLE* molecular subtype is one molecular class that may ultimately be important in endometrial cancer management. Additional studies including multivariate analysis with treatment interactions are necessary to provide confidence that withholding adjuvant therapy for specific subsets of endometrial cancer patients with *POLE* mutations will improve outcomes. The low rates of recurrence and cancer-specific mortality for early stage endometrial cancer patients present a challenge to demonstrating significantly different outcomes for women with *POLE*-mutated tumors. Many ongoing and planned studies include *POLE* testing as part of a broader molecular classification system and thus interpreting data as it relates to *POLE* status alone will be a challenge. Prospective studies demonstrating that women with *POLE*-mutated tumors do not require or benefit from adjuvant therapy are essential. Until such data are available, clinicians and patients must be cautious in utilization of *POLE* molecular findings.

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References

1. Kandoth C, Schultz N, Cherniack AD, Akbani R, Liu Y, Shen H, et al. Integrated genomic characterization of endometrial carcinoma. *Nature*. 2013; 497(7447):67–73. [PubMed: 23636398]
2. Billingsley CC, Cohn DE, Mutch DG, Stephens JA, Suarez AA, Goodfellow PJ. Polymerase varepsilon (POLE) mutations in endometrial cancer: clinical outcomes and implications for Lynch syndrome testing. *Cancer*. 2015; 121(3):386–94. [PubMed: 25224212]
3. Church DN, Stelloo E, Nout RA, Valtcheva N, Depreeuw J, Ter Haar N, et al. Prognostic Significance of POLE Proofreading Mutations in Endometrial Cancer. *J Natl Cancer Inst*. 2015; 107(1)
4. Talhouk A, McConechy MK, Leung S, Yang W, Lum A, Senz J, et al. Confirmation of ProMisE: A simple, genomics-based clinical classifier for endometrial cancer. *Cancer*. 2017
5. Meng B, Hoang LN, McIntyre JB, Duggan MA, Nelson GS, Lee CH, et al. POLE exonuclease domain mutation predicts long progression-free survival in grade 3 endometrioid carcinoma of the endometrium. *Gynecol Oncol*. 2014
6. McConechy MK, Talhouk A, Leung S, Chiu D, Yang W, Senz J, et al. Endometrial carcinomas with POLE exonuclease domain mutations have a favorable prognosis. *Clin Cancer Res*. 2016; 22(12): 2865–73. [PubMed: 26763250]
7. van Gool IC, Eggink FA, Freeman-Mills L, Stelloo E, Marchi E, de Bruyn M, et al. POLE proofreading mutations elicit an antitumor immune response in endometrial cancer. *Clin Cancer Res*. 2015
8. Howitt BE, Sholl LM, Ritterhouse L, Watkins JC, Rodig SJ, Strickland K, et al. Association of *POLE*-mutated and MSI endometrial cancers with an elevated number of tumor-infiltrating and peritumoral lymphocytes and higher expression of PD-L1. *Journal of Clinical Oncology*, 2015 ASCO Annual Meeting (May 29 – June 2, 2015). 2015; 33(15_Supplement):5511.
9. NCCN. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Colorectal Cancer Screening 2017; V.1.2017. Available from: https://www.nccn.org/professionals/physician_gls/pdf/colorectal_screening.pdf
10. Billingsley CC, Cohn DE, Mutch DG, Hade EM, Goodfellow PJ. Prognostic significance of POLE exonuclease Domain mutations in high-grade endometrioid endometrial cancer on survival and recurrence: A subanalysis. *Int J Gynecol Cancer*. 2016; 26(5):933–8. [PubMed: 26937754]