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REVIEW

Endometrial carcinoma diagnosis in the molecular era: a review and new considerations for low- to middle-income countries

J Lunn,[1,2] NH Mbatani,[3,4] MJ Chokoe Maluleke[1,2]

[1] *Division of Anatomical Pathology, Department of Pathology, University of Cape Town, South Africa*
[2] *National Health Laboratory Service, South Africa*
[3] *Department of Obstetrics and Gynaecology, University of Cape Town, South Africa*
[4] *Department of Obstetrics and Gynaecology, Groote Schuur Hospital, Western Cape Department of Health, South Africa*
Corresponding author, email: jackie.chokoemaluleke@uct.ac.za

The incidence of endometrial carcinoma (EC) has seen a steady increase globally over the years. According to the Cancer Association of South Africa (CANSA), EC is the fourth most common carcinoma in women. The publication of the International Federation of Gynecology and Obstetrics (FIGO) 2023 staging for the management of EC has incorporated molecular EC subtyping in addition to commonly used histopathological diagnosis. The four molecular subtypes of EC defined by The Cancer Genome Atlas (TCGA) research group have been renamed: 1) POLEmut (*POLE* ultramutated), 2) p53abn (p53-abnormal, copy number high), 3) MMRd (mismatch repair deficient, microsatellite instability hypermutated), and 4) NSMP (no specific molecular profile, copy number low). The molecular profiling of EC by TCGA used whole exome sequencing with determination of somatic copy number alterations (SCNA) on multiple platforms, which may prove costly in low- to middle-income countries (LMIC). The Proactive Molecular Risk Classifier of Endometrial Cancer (ProMisE) aims to validate TCGA results and investigate the correlation between the traditional clinicopathological prognostic features using a simple decision tree focused on immunohistochemistry and simple molecular testing. In a LMIC healthcare facility, the two molecular subtypes that can be tested using surrogates in immunohistochemical stains are p53 and MMRd, MLH1, PMS2, MSH2, and MSH6. There is no surrogate at present to test for *POLE* mutation; however, there is *QPOLE* – a low-cost quantitative multiplex polymerase chain reaction (PCR) that can detect the 11 most common and pathogenic *POLE* mutations. The use of a flow diagram in the daily clinical practice of patients with EC should be considered in LMIC. Future translational research in determining the cost-effectiveness of preoperative molecular pathology testing for treatment planning and risk stratification of patients is needed in resource-limited settings.

Introduction

Worldwide, endometrial carcinoma (EC) is the fourth most common gynaecological malignancy, with increasing incidences attributed to increasing obesity and sedentary lifestyles, along with other known risk factors, such as metabolic syndrome and ovarian dysfunction. Mortality rates are higher in African Americans compared to white populations in countries like the United States of America.[1]

In South Africa, data on gynaecological malignancies come from the passive surveillance programme of the National Cancer Registry, maintained by the National Health Laboratory Service. In 2020, there were 1 574 histologically confirmed cases of EC recorded, making it the sixth most common cancer diagnosis in South African women, with a lifetime risk of 1 in 144. Markedly, a rising incidence was noted: there were 1 486 cases of uterine cancer in 2018, where uterine cancer was the seventh most common female cancer.[2] This may represent a true increase, or it may represent an improvement in reporting, a growing population of elderly women, or other socioeconomic factors. Regardless, EC is an important cause of morbidity and mortality for South African women.

In the latest World Health Organization (WHO) classification of tumours of the female genital tract, molecular classifications for ECs were introduced after significant advancements in understanding their roles in treatment strategies and prognostication.[3] Subsequently, the International Federation of Gynecology and Obstetrics (FIGO) 2023 staging for ECs reflects this change, which has further implications for practice.[4] In this review, we aim to elaborate on the importance of this development and discuss the application of molecular diagnostics in low- to middle-income settings like South Africa.

Developments in the classification of ECs

The current WHO classification includes several histological EC types, shown in Table I.[3,5] Importantly, most tumours are endometrioid endometrial carcinomas (EEC) and have historically carried a variable but generally favourable

Table I: Subtypes and relative frequency of endometrial carcinoma (EC) subtypes[3]

Endometrioid EC (EEC)	80–90%
Serous carcinoma (SC)	~ 10%
Clear-cell carcinoma (CCC)	< 10%
Carcinosarcoma	~ 5%
Undifferentiated and dedifferentiated carcinoma	~ 2%
Other#	< 1%
Mixed carcinomas	Up to 10%

Includes mesonephric adenocarcinoma, mesonephric-like adenocarcinoma, squamous cell carcinoma and mucinous carcinoma, gastric (gastrointestinal)-type, all primary endometrial origin

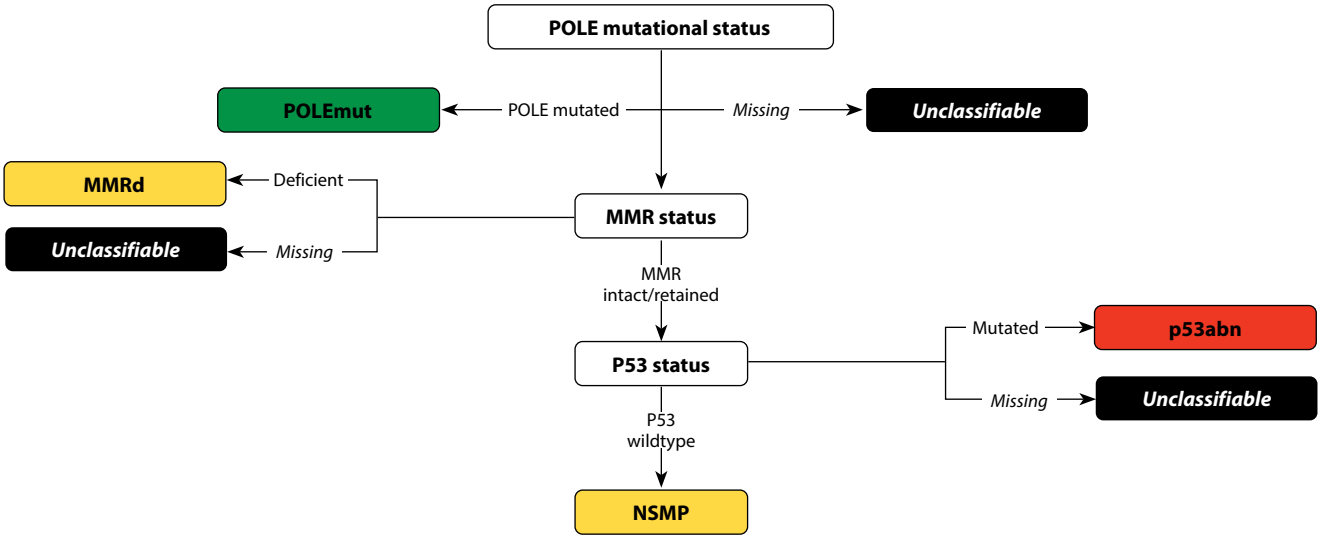


Figure 1: Sequential flow diagram for assessing molecular classification

The *POLE* exonuclease domain mutations must be considered first and, if present, override the presence of mismatch repair (MMR) genes and/or *TP53* mutational status; these POLEmut tumours carry a good prognosis. If no *POLE* mutations are identified, the mutational status of the MMR genes is assessed. If a tumour is deficient (MMRd), the *TP53* gene status is not used for further classification; these MMRd tumours carry an intermediate prognosis. If a tumour shows no POLE mutations nor MMR gene mutation but shows abnormalities in *TP53*, the tumour is classified as p53abn; these carry the worst prognosis. If no aberration is found, the tumour is classified as "no specific molecular profile" (NSMP), which carries an intermediate prognosis. If any particular test cannot be performed, the tumour is automatically "unclassifiable". Adapted from the ProMisE trail.[7,10]

prognosis, with a wide morphological range, shown in Figure 1. Prognostication and choice of treatment have developed over the last 30 years, largely relying on classic histopathological features. Currently, for early-stage cancers, histological type and tumour grade, myometrial invasion, lymphovascular space invasion (LVSI), cervical stromal and any extrauterine disease adnexal involvement, and parametrial/serosal–extension are the most important histologically assessed factors that guide management.[4]

Despite these parameters, variability in clinical outcomes was seen, notably in the heterogeneity amongst high-grade ECs.[4] The underpinnings of this variability were not fully elucidated until the landmark study by The Cancer Genome Atlas (TCGA) identified four molecular classes in ECs based on common oncogenomic architecture.[3,5,6] This molecular classification was a major translational breakthrough as these four molecular groups carried distinctive survival curves, and assessment was performed on preoperative biopsy.[7,8]

The molecular findings by TCGA focused on clustering tumours by somatic copy number alterations (SNCAs), which is the degree of aneuploidy of a tumoral genome. There is abundant evidence for the role of SCNAs in the pathogenesis in > 30 tumour types within TCGA, with evidence for independent effects on treatment and prognosis.[9] Subsequent exome analysis of ECs showed specific molecular driving elements that could be divided into four groups that represented heterogenous clinicopathological findings.[6] These four groups are now referred to in the literature as POLEmut, MMRd, p53abn, and NSMP.

POLE-mutated EC portend an excellent prognosis

The first group identified by TCGA represented those tumours with "ultramutated" genomes, driven by mutations in the *POLE* gene, which encodes deoxyribonucleic acid (DNA) polymerase ε. These tumours carry the highest mutational burden, and although they are the least common molecular group (representing ~ 7% in the original TCGA series), they have an excellent prognosis of up to 100% survival at 60 months.[10-13] Interestingly, in contrast to their favourable prognosis, more than half of these were histologically high-grade tumours, and their indolent nature is not recognised on preoperative specimens, leading to over-treatment in a subset of patients without molecular classification.[6,11,14]

POLEmut shows EEC histomorphology predominantly but can show a wider morphological spectrum with low frequencies of clear-cell and serous carcinomas and carcinosarcomas.[15-17] POLEmut tumours are less likely to have factors associated with poorer outcomes (including higher-stage disease, > 50% myometrial invasion, and positive LVSI), and are also the least prognostically affected by these traditional clinicopathological features.[7,11,18] Of importance is that mixed POLEmut endometrioid-serous carcinomas should be classified as EEC; the divergent morphology is likely a product of the inherent genomic instability of POLEmut tumours, driving the morphological shift.[17]

More than 80% of the pathogenic mutations in *POLE* fall into five hotspots within the gene; mutations at other loci are only pathogenic in ~ 39% of cases.[19] Furthermore, POLEmut status is regarded as the overriding prognostic molecular classifier, even in the presence of "multiple classifiers", namely MMRd and p53abn mutations.[16,17,20] As no immunohistochemical marker for POLEmut status is available, sequencing is the only current means of *POLE* gene assessment.

MMRd EC carry an intermediate prognosis

Tumours with sporadic or germline deficiency of mismatch repair (MMRd) genes present hypermutated genomes with less derangement than that of the POLEmut group, with microsatellite instability.[21] These are the second most common group, representing ~ 28% in TCGA series. Histologically, these

tumours are mostly (~ 85%) endometrioid, and nearly half are high-grade.[14] MMRd is notably frequent in undifferentiated/dedifferentiated carcinomas (~ 44%).[22] Similar to the POLEmut group, there was a low frequency of serous carcinomas and carcinosarcomas. They have an intermediate and more variable prognosis and are more affected by prognostically relevant clinicopathological variables than the POLEmut group.[10]

Histological type seems to play no role in prognostication in this group, apart from some undifferentiated/dedifferentiated MMRd tumours that carry additional mutations in the SWI/SNF chromatin remodelling complex.[23] As with the POLEmut group, morphological and immunohistochemical features of serous carcinoma with MMRd status are classified as EEC.

The four mismatch repair genes are paired (MLH1 with PMS2, and MSH2 with MSH6) and function as heterodimers, consisting of a major and a minor partner. They cannot function without the relevant partner protein, and the loss of the major partners (MLH1 and MSH2) leads to the loss of expression of the corresponding minor partners. Consequently, testing for the minor partners tests for both major and minor partner loss. The current recommendation is to test the minor partners PMS2 and MSH6.[24] Immunohistochemistry is currently recommended for MMRd testing as it is cheaper and faster than molecular assays.[16] Importantly, some MMRd ECs are due to germline mutations (Lynch syndrome), and testing for MMRd is an opportunity to diagnose and screen family members for genetic diseases.

P53abn EC portend the worst prognosis

Tumours without ultra- or hypermutated genomes but where somatic copy number variation is common ("copy number high/serous group"). These tumours are characterised by a high frequency of p53 mutations (~ 85%) and demonstrate serous morphology (~ 73% in the original study).[6] Under old classifications, these tumours represent the "type 2" ECs and have been shown to have analogous demographic profiles.[21] This group represents ~ 25% of tumours and has the worst prognosis.[10] The overwhelming majority of p53abn tumours are high-grade serous carcinomas. This group accounted for nearly three-quarters of the carcinosarcomas and almost half of the clear-cell carcinomas.[6]

P53abn tumours can only be diagnosed when there is no evidence of POLEmut or MMRd.[17] Immunohistochemical testing is sufficiently accurate in detecting *TP53* mutation, with only ~ 5% of p53abn tumours demonstrating no evidence of p53 immunohistochemical aberration.[25]

The NSMP grouping is heterogenous with variable prognosis

The final group demonstrated neither high mutational load nor significant copy number variation as was deemed the "copy number low/endometrioid group". Under old classifications, these tumours represent the "type 1" ECs and are the most frequently encountered, representing roughly 40% in TCGA.[6] These ECs have a variable/intermediate prognosis, with endometrioid morphologies doing better than others.[10] The majority (~ 84%) are low-grade EEC, but any histological type may present as NSMP. This group rarely displays true serous morphology, where misclassification due to the lack of specificity of immunohistochemical markers must be considered.[21]

This group remains a diagnostic category of exclusion, once POLEmut, MMRd, and p53abn have been excluded. However, this group is likely more heterogenous than initially reported, with possible future subclassifications.[21] Given the variability of the NSMP group, several other putative subclassifiers have been investigated. Of note are two markers, *CTNNB1* and *L1CAM*, both have significant and independent effects on recurrence-free survival.[16,21] These are yet to be proven as independent markers.

Cases with multiple classifiers

Occasionally, tumours show multiple classifiers. A hierarchical classification decision tree is shown in Figure 1. POLEmut trumps all, as the POLEmut drives concurrent MMRd/p53abn status. Similarly, MMRd trumps p53abn, as it is the MMRd driving p53 mutation.[20,26] Early follow-up studies have shown similar superior outcomes to those with POLEmut only.[26]

ProMisE trial findings and subsequent large systematic reviews

Proactive Molecular Risk Classifier of Endometrial Cancer (ProMisE) validated TCGA classification and investigated correlation with traditional clinicopathological prognostic features. Using a decision tree derived from the findings of TCGA, the initial and subsequent validation studies showed that classifying by molecular subtype correlated better with overall survival than previously used clinicopathological features, such as tumour grade, positive LVSI, and myometrial invasion. ProMisE showed additional correlates with the molecular classification, including patient morphometric features.[7,10,27]

As shown in Figure 1, all three components (*POLE*, MMR, and *TP53*) are required to classify EC; if one component cannot be tested for, the EC becomes "unclassifiable".[7,10,27] In the ProMisE study, for practical reasons, MMR was performed first as it could be done by immunohistochemistry, allowing rapid referral for those with possible Lynch syndrome, whereas POLEmut testing had a longer turnaround time.

A systematic review has further confirmed the findings of ProMisE. Patients with *POLE* mutations consistently have excellent progression-free and overall survival.[11,13,28] POLEmut status was also protective against lymph node metastasis.[11]

The excellent prognosis of the POLEmut group seems to hold true even for cases with high-grade disease. The prevalence of *POLE* mutations rose to 11% in a recent meta-analysis of high-grade tumours.[28] This high-grade morphology is likely an expression of the ultramutated genome and, interestingly, may portend a survival advantage as a result.[11]

Molecular features are integrated into the FIGO 2023 staging

The FIGO 2023 staging of EC incorporates TCGA molecular classification findings into the staging schema. Staging allows molecular modifiers to be used mainly for stage I and II, highlighting its importance in risk stratifying this group

of patients. Only definitively graded grades 1 and 2 EECs are considered "low-grade", with everything else considered high-grade. Any invasive, high-grade lesion is now at least a stage IIC, except for high-grade lesions limited to a polyp or confined to the endometrium (stage IC). This change reflects the poorer prognosis of these lesions, which are better represented by a higher FIGO stage.[4]

In early endometrial cancer, POLEmut and p53abn now modify the FIGO stage. POLEmut tumours, even in cases with LVSI and cervical stromal extension, are classified as stage $IAm_{POLEmut}$. Any p53abn tumour with any myometrial involvement becomes a stage $IICm_{p53abn}$, including the unusual cases of histologically low-grade tumours with p53 mutations. FIGO stresses the importance of POLEmut and MMRd groups superseding p53abn, echoing the findings of other groups on multiple classifiers.[20] Again, this classification can only be added if a full molecular work-up is done (*POLE*, MMR, and p53).[4] Stage III and IV tumours are not modified by molecular studies in the same way, although this should not preclude molecular studies being performed.

Implications for treatment and adjuvant therapy

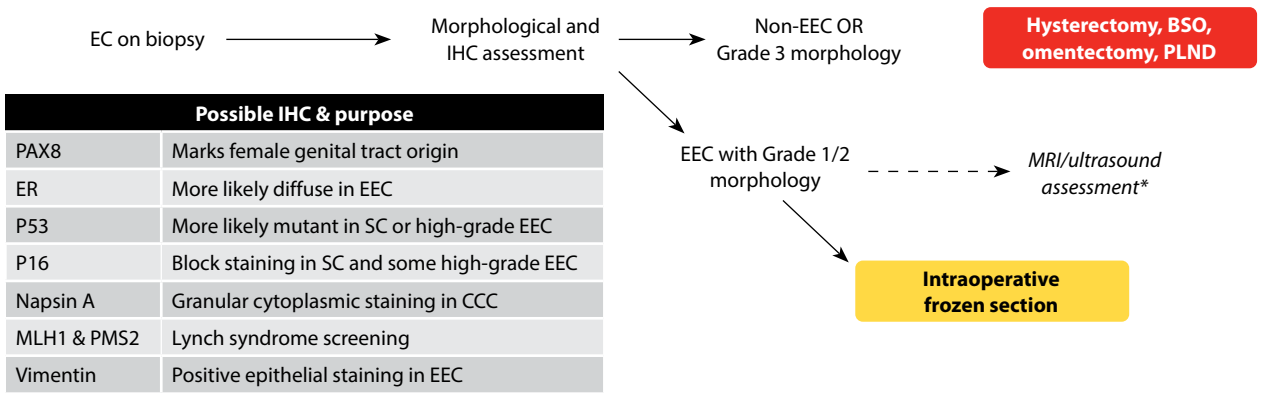
Clinical trials have shown that molecular classification can direct treatment. The PORTEC-3 trial, which classified patients based on histological type and FIGO 2009 staging, showed adjuvant chemotherapy provided no survival benefit during or after radiotherapy (although this did increase failure-free survival).[29] Several studies have shown that omitting adjuvant radiotherapy appears to be safe in stage I POLEmut cases and similarly in stage II cases.[30,31] Of interest, although on a small (n = 29) subgroup of POLEmut stage III/IV disease, only three recurrences (~ 10%) were documented. All these patients received some adjuvant treatment. These, together with other research, support the idea that, at least for some early-stage EC cases, surgery alone may be curative. The PORTEC-4a trial will further elucidate the effect of molecular classification on the need for adjuvant treatment.[32]

Implications of *POLE* mutation status for LMIC

Avoiding the cost of unnecessary adjuvant therapy in POLEmut EC has obvious benefits in LMIC. However, their tendency to show high-grade morphology on preoperative biopsy specimens prompts a more aggressive, upfront surgical approach and likely adjuvant therapy, depending on the risk group.[33] *POLE* testing could benefit FIGO stage IA EEC from less invasive surgery and less intensive postoperative follow-up. Those with IB and IIA/B could receive less invasive surgery, no adjuvant therapy, and less intensive postoperative follow-up.

The benefit to the healthcare system is apparent. Incorporating POLEmut into the diagnostic approach incurs more upfront costs. Nonetheless, testing may offer long-term cost savings by avoiding unnecessary treatments and improving patient outcomes without subjecting them to the adverse effects of adjuvant treatments. Tumours lacking *POLE* gene mutation status can be further classified, as per Figure 1, and receive the necessary care, which may also carry long-term cost savings.

A



Possible IHC & purpose	
PAX8	Marks female genital tract origin
ER	More likely diffuse in EEC
P53	More likely mutant in SC or high-grade EEC
P16	Block staining in SC and some high-grade EEC
Napsin A	Granular cytoplasmic staining in CCC
MLH1 & PMS2	Lynch syndrome screening
Vimentin	Positive epithelial staining in EEC

B

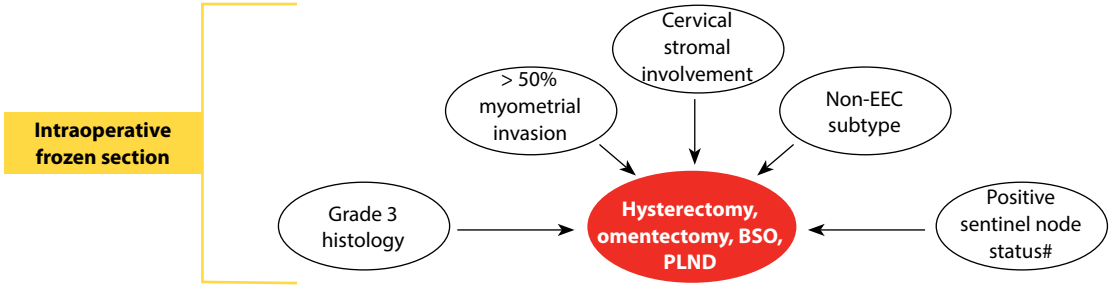


Figure 2: Practices at our centre

A. After histological classification using various immunohistochemical markers in the table, ECCs are graded. Grade 1 and 2 tumours are then selected for frozen section (* or imaging modalities, currently under investigation).
B. At frozen section, various features will determine the extent of surgical intervention. If all of these are absent, a simple hysterectomy with or without BSO is done (# note that our centre sentinel node status is currently not practised).

BSO – bilateral salpingo-oophorectomy, CCC – clear-cell carcinoma, EC – endometrial carcinoma, EEC – endometrioid endometrial carcinoma, IHC – immunohistochemistry, MRI – magnetic resonance imaging, PLND – pelvic lymph node dissection, SC – serous carcinoma

The practice at our centre (Groote Schuur Hospital/University of Cape Town) is shown in Figure 2A as an example. Briefly, morphological and immunohistochemical assessment is used on endometrial samples to assist with surgical planning (including pelvic lymph node dissection [PLND]). For samples with low-grade tumours, frozen sections or magnetic resonance imaging are requested to decide on the need for PLND. The factors at frozen section that change management are shown in Figure 2B. Although our practice assesses for p53 mutations and MMR, we do not assess for POLEmut status. Thus, all tumours we test are considered "unclassifiable"; immunohistochemistry aids histological typing.

Each immunohistochemical marker done at our laboratory costs approximately ZAR 600 (~ USD 30 at the time of writing), and the cost of ancillary testing alone, per case, may be upwards of ZAR 4 000 (~ USD 210) depending on the extent of molecular typing. This may be significantly more expensive in private services. Adding molecular testing could significantly increase this cost; POLEmut testing requires next-generation sequencing (NGS) for EEC, which costs approximately ZAR 13 000 (~ USD 680) through current providers. As cautioned in international settings, because of the added cost, we acknowledge that the addition of molecular testing in EC must be carefully considered in LMIC.[34]

The expense of NGS in this context has long been recognised, with particular concern for low-resource settings. Consequently, the ProMisE trial used more cost-effective, directed sequencing methodologies, making testing more accessible. They did this by focusing on mutations in the exonuclease domain of *POLE*. Indeed, selective sequencing detects between 67% and 92% of POLEmut carcinomas.[8,12,35] Given that 80% of pathologically significant mutations occur in the exonuclease domain, these more cost-effective methodologies could be applied in LMIC. These targeted platforms currently carry a cost of approximately ZAR 4 000–5 000 (USD 210–260) per test, making them more accessible in our setting with an acceptable identification rate.

The potential savings by avoiding the over-treatment of POLEmut patients are multifaceted and difficult to precisely estimate in this review. The various costs include the unnecessary frozen section, the additional anaesthetic and theatre time on already pressured theatre lists whilst awaiting the frozen section report, and/or performing PLND, adjuvant therapy, and long-term clinic follow-up. All these factors carry one additional common cost: avoidable patient morbidity and mortality. Balancing cost-effective care with good patient outcomes remains complex in healthcare delivery.

Future research considerations in the African setting

Given the availability of more affordable, directed *POLE* exonuclease testing, multidisciplinary teams should consider the implementation of molecular profiling for EEC. However, consideration of our unique demographics is important prior to changing practice.

The prevalence of patients with POLEmut status in our setting is unknown. International studies and pooled data suggest prevalences between 7% and 11%.[11,13,28] White populations are largely over-represented in much of the available data.[36,37] Indeed, in a recent meta-analysis, only 10% of the cohort were identified as black and consisted predominantly of African Americans.[37] There is established evidence that EC is more common in Caucasian populations, whereas black patients present with more advanced disease and poorer-prognosis histological types, with overall poorer survival.[36] There are likely both socioeconomic and genetic differences underlying this. Of interest are the recent findings that, although *POLE* mutations were less frequent in black patients, *POLD1* mutations were more frequent, and survival of *POLD1* and *POLE* mutations had similarly excellent outcomes.[37] Investigations into the prevalence and precise genomic profile of our population would aid further motivation for testing.

With novel *POLE* sequencing methodologies showing increased cost-effectiveness, such as directed sequencing using standard quantitative PCR methods (and not proprietary NGS methods requiring specific equipment), it is plausible that these methodologies will become more cost-effective, can be designed "in-house" by laboratories or central testing centres, and can also be adaptable to our unique genomic setting.[35] Collaboration between local healthcare services and industry service providers may further aid in cost-effective molecular testing.

Concurrently, the overall cost-effectiveness of molecular testing in the holistic treatment of a patient in our setting must be investigated, given that the molecular class changes the degree of intervention. Encouraging work has shown cost-effectiveness to molecular classification in early-stage, high-risk EC, and women with postmenopausal bleeding and minimally invasive EC, with overall decreases in costs to the healthcare system.[38,39] This data is encouraging, and similar studies are paramount in collaboration with health economics and policymakers.

Importantly, given the higher prevalence of Lynch syndrome in South Africa, adopting a molecular classification for EEC may assist in Lynch syndrome detection.[40,41] Moreover, if available resources are compatible, standard MMR testing would add population benefit.

Conclusion

The era of precision diagnostics in EC brings with it opportunities for better patient stratification, medical and surgical care, and prognostication. This stratification may be helpful in our setting by identifying patients who do not require extensive surgical intervention, adjuvant therapies, and extended follow-up, thus decreasing pressure on clinical services. However, the current distribution and prevalence of each TCGA category amongst African populations remains unknown and are a focus of study at several centres. Indeed, knowing our genomic landscape will aid in decision-making around precision diagnostics in EEC and will support patient equity within a resource-limited setting.

Conflict of interest

The authors declare no conflict of interest.

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ORCID

J Lunn https://orcid.org/0009-0006-1843-3236
NH Mbatani https://orcid.org/0000-0001-8826-5182
MJ Chokoe Maluleke https://orcid.org/0000-0001-7017-7424

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