The British Association of Gynaecological Pathologists

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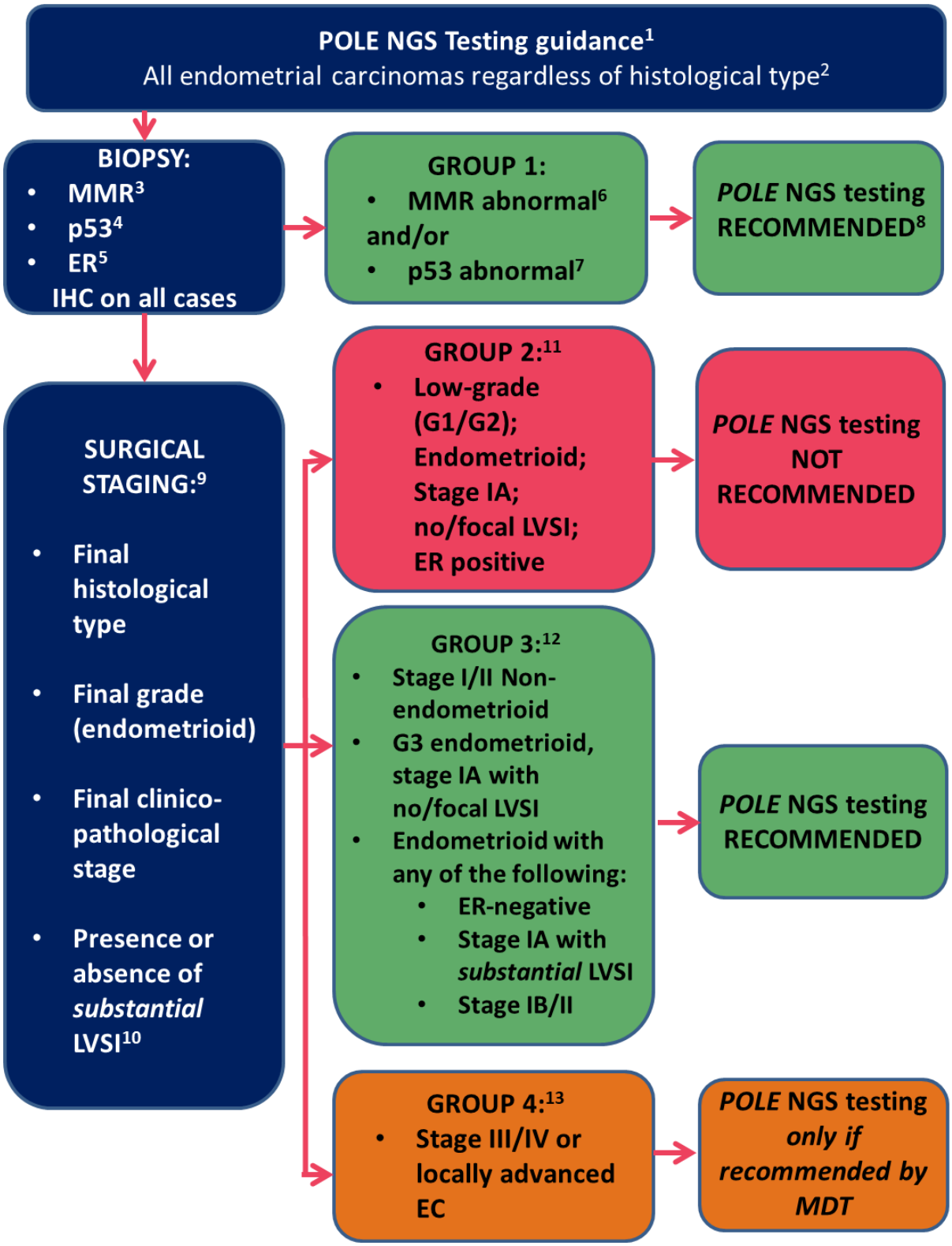

BAGP *POLE* NGS testing guidance, v1.1, dated 8 April 2022

Authors: Naveena Singh[1,2], Amy Jamieson[2], Jo Morrison[3], Alexandra Taylor[4], Raji Ganesan[5]

[1]Barts Health NHS Trust, London, UK, [2]Vancouver General Hospital, Vancouver, Canada; [3]Musgrove Park Hospital, Taunton, UK; [4]Royal Marsden Hospital, London, UK; [5]Birmingham Women's Hospital, Birmingham, UK

BAGP guidance on *POLE* NGS testing in endometrial carcinoma

GLOSSARY:

EC: Endometrial carcinoma

G1/G2/G3/low-grade/high-grade: FIGO grades of endometrioid carcinoma; note that this grading system does not apply to non-endometrioid histotypes which are broadly classified as 'high-grade'

Histotype: Histological type of EC categorised on morphological features as defined by the WHO

IHC: Immunohistochemistry

LVSI: Lymphovascular space invasion

MMR: Mismatch repair

NGS: Next Generation Sequencing

NSMP: No Specific Molecular Profile, i.e. EC that no not show MMR, p53 or POLE defects

POLE: DNA polymerase epsilon

Stage: FIGO or TNM staging of EC

WHO: World Health Organisation (specifically the classification of female genital tumours, 5th edition, 2020)

Note 1: *POLE* NGS testing in endometrial carcinoma

Molecular testing in endometrial carcinoma, including mutational analysis for *POLE,* is recommended by the World Health Organisation wherever resources permit[1]. *POLE* NGS testing will soon be available for NHS patients via national genomics services within the UK. This requires considerable resources and additional work for laboratories in sample preparation and transport, sample analysis and provision of an integrated report. This algorithm is provided to limit *POLE* testing to those cases where it is essential for patient care. This is meant to be a guideline and it is appreciated that centres may follow local policy on the extent of testing and opt to further minimise and restrict testing to only those cases where the *POLE* result alters decisions regarding adjuvant treatment, or at the other extreme, move to universal testing of all cases. Interpretation of *POLE* results should be based on published data[2]: 11 mutations have been established as being pathogenic, with the variants in bold accounting for the majority of cases: **P286R (c.857C>G), V411L (c.1231G>T/C), S297F (c.890C>T),**

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S459F (c.1376C>T), A456P (c.1366G>C), F367S (c.1100T>C) L424I (c.1270C>A), M295R (c.884T>G), P436R (c.1307C>G), M444K (c.1331T>A) and D368Y (c.1102G>T).

Non-pathogenic variants and guidance for determining the pathogenicity of additional variants has also been put forward[2].

Note 2: Testing of all endometrial carcinoma biopsies regardless of histotype

Following the discovery of the four molecular subtypes of endometrial cancer (EC) by The Cancer Genome Atlas (TCGA) in 2013[3], the **Pro**active **M**olecular R**is**k Classifier for **E**ndometrial Cancer (**ProMisE**) was developed and validated for clinical use[4-6]. This uses a combination of targeted sequencing for pathogenic *POLE* exonuclease domain mutations and immunohistochemistry (IHC) to determine MMR and p53 status, to assign EC to one of four molecular subtypes; *POLE*mut, MMRd, p53abn, and NSMP (no specific molecular profile). Molecular classification of EC has since been shown to have a stronger prognostic significance than conventional histological classification[4-8]. Historically, the EC risk stratification used to guide treatment has largely been based on histological type, grade, and stage. Both histotype and grade assignment have been shown to be poorly reproducible, even amongst expert pathologists, with no agreement in histotype diagnosis in up to one third of cases[9-11]. In contrast, EC molecular classification has been shown to be highly reproducible and can be accurately performed on endometrial biopsies, with high concordance between biopsy and final hysterectomy specimen[12,13]. The 2020 5th edition of the WHO Female Genital Tumours recommends the integration of molecular classification into standard EC pathology reporting[1]. While the assessment of MMR and p53 IHC are widely available, cost and access to *POLE* testing currently presents a major barrier to widespread adoption. This algorithm presents a way of restricted use of *POLE* testing to patients whom *POLE* status would impact on treatment decisions.

Note 3: MMR IHC should be performed on all endometrial cancers

As recommended by NICE in October 2020 (Diagnostics guidance DG42 available at: Overview | Testing strategies for Lynch syndrome in people with endometrial cancer | Guidance | NICE), all patients diagnosed with EC should have screening for Lynch syndrome[14]. The initial step is four-panel IHC testing for MMR deficiency (MLH1, MSH2, MSH6 and PMS2). If the IHC is abnormal, with loss of MLH1 +/- PMS2, MLH1 promoter hypermethylation testing on tumour DNA should be performed to differentiate sporadic and Lynch syndrome-associated cancers. If loss of MSH2, MHS6, or isolated PMS2 is found on IHC, germline testing for Lynch syndrome is recommended[14]. Identification of mismatch repair deficient (MMRd) EC also has important therapeutic implications. Defects in mismatch repair lead to a high mutational burden, an abundance of neoantigens and profound immune response, making these ECs an ideal target for immune checkpoint blockade (ICB) therapy. The 2017 FDA approval for ICB therapy in MMRd solid tumours has been followed by multiple single agent EC clinical trials with PD-1 and PD-L1 inhibitors showing response rates of 49-57% and 27-43%, respectively, in MMRd advanced, metastatic or recurrent ECs[15].

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Note 4: p53 IHC should be performed on all endometrial cancers

p53abn EC represent the most aggressive molecular subtype, and account for majority of EC mortality[16]. The ECs in this molecular subtype were characterised by TCGA as having a very high number of somatic copy number alterations, low mutation rate, and ubiquitous *TP53* mutations[3]. These tumours are now identified by a more pragmatic method of mutant-pattern p53 IHC staining, which has been shown to be an excellent surrogate maker for *TP53* mutational status as determined by sequencing in EC biopsies[17]. Recent evidence has shown the p53abn molecular subtype is found in up to 5-10% of grade 1 and 2 endometrioid ECs[16,18-20]. The 2020 ESGO/ESTRO/ESP guidelines classify any stage p53abn EC with myoinvasion, regardless of the grade or histotype, as high-risk disease, with a recommendation for adjuvant chemotherapy +/- radiation[21]. The value of carrying out universal p53 IHC is to avoid missing cases of serous carcinoma that may mimic endometrioid carcinoma, as well as identifying the infrequent p53abn EC cases that show endometrioid grade 1 or grade 2 histology.

Note 5: ER IHC should be performed on all endometrial cancers

The category of NSMP EC is one of exclusion, namely all those EC that do not harbour mismatch repair defects or pathogenic *POLE* or *TP53* mutations. This is a large and heterogeneous group that accounts for about 50% of all EC. Studies on biomarkers of poor outcome in this category have thus far been inconclusive, however, ER status and presence of LVSI. The value of universal ER testing is to indicate the possibility rarer histotypes of EC that may closely mimic endometrioid EC, such as clear cell, mesonephric-like and gastrointestinal-type mucinous EC; these are negative for ER, in contrast to the generally strong positivity typical of endometrioid EC. In addition, knowledge of ER status may help to inform decisions on hormonal treatment including hormone replacement therapy. Most importantly, ER status has been demonstrated to correlate with recurrence-free survival in NSMP EC[22]; notably in this analysis a cut-off of 10% was applied and thereby flat negative or very focal ER expression should alert the pathologist to the possibility of a non-endometrioid histotype or potential for aggressive behaviour in an endometrioid tumour.

Note 6: Interpretation of MMR IHC

MMR status should be reported as normal or abnormal, with an appropriate message relating to the likelihood of Lynch Syndrome and thereby recommendation for referral to clinical genetics services. MMR IHC interpretation and reporting terminology have been the subject of previous BAGP guidance[23].

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Note 7: Interpretation of p53 IHC

IHC results of p53 should be reported as normal or abnormal (aberrant or mutation-type are appropriate alternatives). Reporting as 'positive' or 'negative' should be avoided. Pathologists should be familiar with the abnormal staining patterns: over-expression, complete absence (also known as 'null'), cytoplasmic and subclonal, as distinct from normal or 'wild-type' p53 expression. This has been the subject of previous BAGP guidance[24], an online teaching resource for p53 interpretation in EC (Interpretation of p53 Immunostaining in Endometrial Carcinoma (ubc.ca))and detailed reviews[25,26].

Note 8: *POLE* testing in the presence of abnormal MMR and/or p53 IHC

Given the high mutational burden observed in *POLE*mut and MMRd tumours, secondary *TP53* mutations/p53 IHC abnormalities can be found. Leon-Castillo *et al* reported on the approximately 3-5% of ECs that have more than one molecular feature, called 'multiple classifiers'[27]. They demonstrated that MMRd-p53abn tumours have morphology, molecular profiles and clinical behaviour aligning with MMRd EC, and the *POLE*mut-p53abn EC have morphology, molecular profiles and clinical behaviour aligning with *POLE*mut EC. These findings suggest the *TP53* mutation is a later event during tumour progression in *POLE*mut and MMRd tumours and does not affect the clinical outcome[27]. This also highlights the importance of interpreting p53 and MMR IHC in the context of *POLE* mutation status to avoid overtreatment in these patients with 'multiple classifiers'. The 2020 ESGO/ESTRO/ESP guidelines for the management of patients with EC classify stage I-II *POLE*mut EC as low-risk and omission of adjuvant therapy should be considered[21].

Note 9: Surgical staging including hysterectomy

FIGO staging for EC is surgical[28]. Standard surgery consists of a total hysterectomy and bilateral salpingo-oophorectomy, and there is high level evidence supporting a minimally invasive surgical approach[29,30]. Sentinel lymph node biopsy has been shown to have a high diagnostic accuracy in EC, and is now recommended to be performed over full lymphadenectomy[14]. Indications for nodal assessment in EC varies significantly between centres. The British Gynaecological Cancer Society (BGSC) recommends that surgical staging, including sentinel lymph node biopsy and omental biopsy, may be appropriate for women with disease greater than low risk[14]. For patients with known stage II EC, total hysterectomy and bilateral salpingo-oophorectomy is still recommended, and radical hysterectomy should only be performed if required to obtain tumour free margins[14,21]. Further in-depth discussion regarding surgical staging in EC is beyond the scope of this document.

Note 10: Lymphovascular space invasion (LVSI) in EC

Lymphovascular space invasion (LVSI) is an established prognostic indicator in endometrial carcinoma and influences ESGO-ESTRO-ESP risk categorisation[21]. A binary distinction between no or focal LVSI as opposed to extensive/substantial LVSI is recommended but the cut-off has varied: previous recommendations by the International Society of Gynecological Pathologists defined 'extensive' LVSI

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as the presence of three or more vessels containing tumour[31], while the 2020 WHO Classification and ESGO-ESTRO-ESP guidelines state the presence 5 or more involved vessels being definitional for extensive/substantial LVSI[1,21]. The International Collaboration on Cancer Reporting dataset recommends: "Although there have been different proposals for what constitutes extensive LVI, it is a good rule of thumb to diagnose extensive LVI when it is easily recognisable at scanning magnification (and artefact is excluded) and when present in three or more vessels on closer inspection" .[32]

Note 11: No *POLE* testing is indicated for low grade (grade 1 or 2) endometrioid, stage IA, no LVSI, and normal MMR and p53 IHC

Talhouk *et al* recently validated an amended ProMisE testing protocol where p53 and MMR IHC were performed on all cases with omission of *POLE* sequencing in 'very low-risk' EC[33]. These were defined as cases fulfilling all of the following: grade1/2, MMR-proficient, p53 wild-type, endometrioid histology, stage IA, no LVSI. The rationale for omitting *POLE* testing in this 'very low-risk' subgroup is because the clinical outcomes are excellent, with no adjuvant therapy required, thus *POLE* status would not alter management of these patients. In this validation series they did confirm this 'very low-risk' EC cohort with unknown *POLE* mutational status had excellent clinical outcomes, comparable to that of ECs known to have pathogenic mutations in *POLE.*

Note 12: *POLE* testing is recommended in Stage I-II non-endometrioid EC or any grade endometrioid stage IA with LVSI or stage IB /stage II regardless of LVSI

The majority of *POLE*mut ECs are endometrioid, and despite many having high-risk features, such as high-grade and LVSI, this molecular subtype has exceptionally favourable survival outcomes[4-8]. A recent meta-analysis which included 294 patients with pathogenic *POLE* mutations showed that the excellent survival outcomes of stage I/II *POLE*mut EC was independent of adjuvant treatment received[34]. There are two clinical trials currently assessing the safety of de-escalation of adjuvant treatment in *POLE*mut EC (PORTEC-4a and TAPER- **T**ailored **a**djuvant therapy in ***P****OLE*-mutated and p53-wildtype early stage **e**ndometrial cance**r**) and a third will be commencing shortly (the TransPORTEC RAINBO Blue-*POLE* arm). The 2020 ESGO/ESTRO/ESP guidelines classify stage I-II *POLE*mut EC as low risk and state that in women with Stage I-II pathogenic *POLE*mut ECs, omission of adjuvant therapy should be considered[21]. We therefore recommend testing *POLE* status in patients where the recommended adjuvant therapy would change if a pathogenic *POLE* mutation is found:

- Stage I-II non-endometrioid ECs
- Any grade endometrioid stage IA with LVSI, grade 3 endometrioid stage IA with no/focal LVSI, or any grade endometrioid stage IB/stage II regardless of LVSI

Identification of pathogenic *POLE* mutations in these patients will allow discussion of de-escalation of adjuvant therapy and/or identify patients eligible for de-escalation clinical trials and these patients may be spared the toxicity and cost of unnecessary radiation treatment +/- chemotherapy.

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Note 13: *POLE* testing is not indicated in Stage III-IV EC unless directed by MDT and/or patient choice

There is currently insufficient evidence to guide adjuvant treatment of advanced stage (III-IV) *POLE*mut EC. Furthermore, the 2020 EGSO/ESTRO/ESP EC treatment recommendations for stage III-IV EC are the same regardless of molecular subtype[21], therefore *POLE* status would not currently alter management in these patients.

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