FIGO 2023 endometrial cancer staging: too much, too soon?

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ABSTRACT
An updated International Federation of Gynecology and Obstetrics (FIGO) staging system for endometrial carcinoma was introduced in June 2023. The new system represents a significant departure from traditional endometrial and other gynecological carcinoma staging systems which are agnostic of parameters such as tumor type, tumor grade, lymphovascular space invasion, and molecular alterations. The updated system, which incorporates all of these ‘non-anatomical’ parameters, is an attempt to make staging more personalized and relevant to patient prognostication and management, and to align with the European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology (ESGO/ESTRO/ESP) risk stratification. Herein, we present a critical review of the new staging system and discuss its advantages and disadvantages. The authors propose that the new FIGO staging system should be first appraised at a multi-institutional and global level with the input of all relevant societies (gynecology, pathology, gynecologic oncology, medical oncology, radiation oncology) to understand the impact, scope, and supporting evidence of the proposed changes. Such a process is fundamental to produce a robust system that pathologists and treating clinicians can adopt.

INTRODUCTION
In June 2023, the International Federation of Gynecology and Obstetrics (FIGO) Women's Cancer Committee officially introduced an updated staging system for endometrial carcinoma to replace the last 2009 update.1,2 The new staging system is markedly different from prior versions by shifting the concept of ‘stage’, traditionally an indicator of anatomic tumor spread, to include several pathological parameters such as tumor type, tumor grade, lymphovascular space invasion (LVI), and molecular alterations. The new system is presented as an attempt to make staging more personalized and relevant by incorporating critical determinants of patient management into staging. Herein, the authors present a critical evaluation of the new FIGO staging system for endometrial carcinoma, discuss its advantages and disadvantages, including a significant lack of pathology input, and provide suggestions for improvement. We believe that future discussion, paired with critical appraisal of the current evidence and reflection on local resources and healthcare needs, is needed before adoption of the new FIGO staging system.

TRADITIONAL STAGING, RISK GROUPS, AND NEW STAGING TRENDS
Traditional cancer staging is a statement of the anatomical extent of disease at the time of presentation, determined by clinical, pathological, and radiological information. Stage is a key prognostic factor, often being the strongest predictor of patient outcome. The globally accepted method for cancer staging is the Tumor, Lymph Node, Metastasis (TNM) system, first devised by French surgeon Pierre Denoix in the 1940s.3 The main bodies for cancer staging are the American Joint Committee on Cancer (AJCC) in the USA, and the Union for International Cancer Control (UICC) in Europe. The first AJCC cancer staging manual was published in 1977, and from the 1980s a joint agreement between these bodies has ensured worldwide access to simultaneously published and concordant editions of the AJCC Cancer Staging Manual and the UICC TNM Classification of Malignant Tumours.4,5 A similar collaborative arrangement with FIGO ensures comparability, with updates to FIGO staging generally incorporated into both the AJCC and UICC versions.6

While the anatomic extent of disease remains the foundation for tumor staging, the sixth (2002), seventh (2009), and eighth (2017) editions of the AJCC staging manual have progressively transitioned to staging systems that include histologic prognostic factors, biomarkers, and molecular data.7,8 Examples where this has occurred include staging of breast, head and neck, and prostatic carcinomas, although most staging systems do not use these non-anatomic parameters.7,8 This integrated approach aims to maintain the clinical relevance of staging by improving its prognostic value, ultimately leading to improved clinical decision making.7,8 A similar concept has taken the form of ‘risk stratification’, in which different clinical and pathological variables (stage being one) determine the ‘risk’ group which then determines prognosis and patient management. The European Society of Gynaecological Oncology/European Society for
for Radiotherapy and Oncology/European Society of Pathology (ESGO/ESTRO/ESP) guidelines for the management of patients with endometrial cancer are a prime example of this concept.5

APPRAISAL OF THE 2023 FIGO STAGING UPDATE

Summary of Major Changes
The FIGO 2023 update builds on its 2009 predecessor which, like most other staging systems, is based on anatomic distribution of disease within the organ of origin and beyond. Table 1 is a comparison between the 2009 FIGO staging system, which currently is synonymous with the AJCC eighth edition staging system, and the 2023 FIGO system. The most important differences are the introduction of non-anatomical parameters in stage I and II cancers (specifically histological type and grade, LVSI, and molecular group), and subdivision of stage III and IV categories according to location (vaginal vs parametrial) and size (nodal micrometastasis vs macrometastasis) of disease. Another major change is the separation of patients with uterine corpus and ovarian involvement into two categories: those with a supposed good prognosis based on criteria traditionally attributed to ‘synchronous’ malignancy (stage IA3), and those with uterine and/or ovarian tumor characteristics portending worse behavior (stage IIIA1). The former were traditionally viewed as representing synchronous independent malignancies, although molecular studies have now proven most to be clonal and to represent ovarian metastasis from the uterine primary; these are thought to have a better prognosis, although there is a paucity of studies with follow-up.10 11

There are also some important divergences between 2023 FIGO and the 2021 ESGO/ESTRO/ESP guidelines. First, ESGO/ESTRO/ESP separates high-grade (FIGO grade 3) endometrioid carcinoma from non-endometrioid carcinomas, while 2023 FIGO groups these two categories as ‘aggressive histological types’. Second, in both systems POLE mut and p53abn molecular groups affect risk/stage. The same does not apply to mismatch repair (MMR) deficient and no specific molecular profile (NSMP) molecular groups. These serve to stratify tumors into intermediate, intermediate-high, and high-risk ESGO/ESTRO/ESP categories but are not included in 2023 FIGO.

Advantages of New Staging System
The FIGO 2023 staging update does have strengths worthy of mention. It is acknowledged that endometrial carcinoma is not a single disease, and that parameters important for management and prognostication should be incorporated into a functional algorithm. The new FIGO system expands the categorization of stage II, stage III, and stage IV disease to account for different types of uterine and extraterrorine cancer spread, which will help accrue data on their prognostic and therapeutic significance. Worthy of mention is the inclusion of nodal involvement categories based on metastatic tumor size, in line with the approach taken by AJCC to stratify nodal disease in gynecological and many other cancers. Likewise, the separation of tumors with synchronous involvement of the uterine corpus and ovary and favorable outcome is important to tailor patient management and avoid overtreatment.

Disadvantages of New Staging System
One major concern with the 2023 FIGO system is that it is markedly different and perhaps more complicated than the prior version, which is likely to hinder adoption, translation, and generalization. This will make comparisons between prior and new patient cohorts extremely difficult and will result in challenges in compiling data for clinical, epidemiologic, and research (particularly clinical trial) purposes.

Premature Use of Evolving and Controversial Variables
Another disadvantage of the new FIGO system is the premature incorporation of variables for which definitions are still evolving, as well as variables that are subject to considerable interobserver variability in their assessment. Many cancer care guidelines and reporting resources model on FIGO. Two major examples are the College of American Pathologists (CAP) reporting tools and the AJCC staging. Controversial and poorly reproducible variables introduced in the 2023 update will be translated to those guidelines, greatly impacting patient care. One illustrative example is the requirement to distinguish between a superficially myoinvasive tumor and one confined to the endometrium. This distinction is problematic, particularly in the setting of non-aggressive (low-grade endometrioid) cancers, as it is known to suffer from poor interobserver agreement due to various factors such as the often irregular endometrial/myometrial interface and the presence of adenomyosis, which when involved by tumor can be difficult to separate from true myoinvasive disease.12 13

Another potentially controversial variable introduced by the 2023 FIGO is tumor involvement of ‘uterine subserosa’, mentioned in the publication as a criterion for stage IIIA2 but not defined in a way that can be reproducibly evaluated by the pathologist. The International Society of Gynecological Pathologists (ISGyP) recommendations already include the submucosal fibroconnective tissue as part of the definition of serosal involvement.14 The concept of uterine subserosal (different from serosal) invasion is not included in any current staging system, scientific guideline or reporting resource document, and will cause interpretation issues.

A histologic variable still in evolution and without concrete reproducible agreement is quantification of LVSI, and several different definitions are in use. FIGO 2023 uses involvement of five or more lymphovascular spaces to define substantial (extensive) LVSI, as does the 2020 WHO Classification of Female Genital Tumors16 and the ESGO/ESTRO/ESP management guidelines.5 Other resources use different definitions for substantial LVSI—for example, four or more spaces in at least one hematoxylin and eosin (H&E) slide in the National Comprehensive Cancer Network (NCCN) guidelines,15 and three or more spaces in the 2023 International Collaboration on Cancer Reporting (ICCR),16 the 2019 ISGyP Endometrial Cancer Project recommendations,12 and the 2023 CAP cancer reporting protocol.17 Most resources, including the 2023 FIGO update, do not clarify whether the extent of LVSI is based on the maximum involvement in a single tissue section or on the cumulative extent across all tissue sections. In light of these multiple definitions and overall lack of clarity, the reproducibility of LVSI quantification remains to be fully documented. This may lead to potential difficulties in comparability between practices and regions. For example, if one center has a very rigorous approach and a high threshold for diagnosis of substantial LVSI, a stage drift compared with other centers will develop. This will result in differing outcomes between centers, stage by stage, not due to real differences in patient outcome, but
Table 1  Comparison of FIGO 2009 and FIGO 2023 staging systems for endometrial carcinoma

<table>
<thead>
<tr>
<th>FIGO 20092 (AJCC 8th ed)</th>
<th>FIGO 2023</th>
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<tbody>
<tr>
<td><strong>Stage I</strong></td>
<td></td>
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<tr>
<td>Defined as tumor confined to the uterine corpus.</td>
<td>Defined now by a combination of the following features: histological type(^a), myometrial invasion (presence and extent into inner vs outer half), absent or focal LVSP(^b).</td>
</tr>
<tr>
<td>Subdivided as IA (myometrial invasion absent or &lt;50% of the uterine wall) and IB (myometrial invasion ≥50%).</td>
<td>Categorization as IA vs IB as defined in FIGO 2009(^2) now only applies to non-aggressive histological types with no or focal LVSI.</td>
</tr>
<tr>
<td>Distinction between absent and &lt;50% myometrial invasion is not necessary.</td>
<td>For non-aggressive histological types with no or focal LVSI, reintroduces distinction between cancer confined to the endometrium (now IA1) vs &lt;50% myometrial invasion (now IA2) vs ≥50% myometrial invasion (IB).</td>
</tr>
<tr>
<td>For aggressive histological types, introduces stage IC (aggressive histological types without myometrial invasion), and considers any myometrial invasion as stage IIC.</td>
<td></td>
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<tr>
<td>Introduces ovarian involvement as allowed if the following criteria are present: low grade endometrioid type; absent or superficial myometrial invasion (&lt;50%); absent or focal LVSI; absence of additional metastases; the ovarian tumor is unilateral, limited to the ovary, without capsule invasion/rapture.</td>
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<tr>
<td><strong>Stage II</strong></td>
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<tr>
<td>Defined as tumor confined to the uterus with invasion into the cervical stromal tissue.</td>
<td>Defined now by a combination of the following features: cervical stromal involvement, substantial LVSI(^b), and aggressive histological tumor type with myometrial invasion.</td>
</tr>
<tr>
<td>Stage II is now subdivided into IIA (cervical stromal invasion by non-aggressive histological type), IIB (substantial LVSI by non-aggressive histological type), and IIC (aggressive histological type with any myometrial invasion).</td>
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<tr>
<td><strong>Stage III</strong></td>
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<tr>
<td>Defined as spread outside of the uterus other than bladder/intestinal lining, lymph nodes, and distant sites.</td>
<td>Defined as local and/or regional tumor spread.</td>
</tr>
<tr>
<td>Groups tubo-ovarian and serosal tumor involvement as stage IIIA.</td>
<td>Stage IIIA is now subdivided into IIIA1 (spread to ovary or fallopian tube) and IIIA2 (involvement of uterine subserosa or spread through uterine serosa). Introduces the concept of ‘uterine subserosa’.</td>
</tr>
<tr>
<td>Defines vaginal and parametral tumor involvement as stage IIIB.</td>
<td>Stage IIIB now includes pelvic peritoneum. It is subdivided into IIIB1 (metastasis or direct spread to vagina and/or parametra) and IIIB2 (metastasis to pelvic peritoneum).</td>
</tr>
<tr>
<td>Groups nodal micro- and macrometastasis as stage IIIC1 (pelvic) and IIIC2 (para-aortic).</td>
<td>Stage IIIC1 (pelvic nodal spread) is now subdivided into IIIC1i (micrometastasis) and IIIC1ii (macrometastasis). Stage IIIC2 (para-aortic nodal spread) is now subdivided into IIIC2i (micrometastasis) and IIIC2ii (macrometastasis).</td>
</tr>
<tr>
<td><strong>Stage IV</strong></td>
<td></td>
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<tr>
<td>Groups abdominal peritoneal spread along with lungs, liver, brain, bone, and inguinal or extrapelvic lymph nodes above renal vessels (stage IV B).</td>
<td>Separates abdominal peritoneal spread (now IVB) from lungs, liver, brain, bone, and inguinal or extrapelvic lymph nodes above renal vessels (stage IV C).</td>
</tr>
</tbody>
</table>

\(^a\)Histological types:
- Non-aggressive histological types: FIGO grade 1 and 2 endometrioid.
- Aggressive histological types: FIGO grade 3 endometrioid, serous, clear cell, undifferentiated, dedifferentiated, mesonephric-like, gastrointestinal-type mucinous, carcinosarcoma.

\(^b\)Lymphovascular space invasion (LVSI):
- Substantial: ≥5 vessels involved.
- Focal: <5 vessels involved.
to systematic differences in stage assignment (the so-called ‘stage migration effect’). The existence of a subset of patients with low-grade endometrioid carcinoma confined to the uterine corpus and ovary who have a favorable outcome is recognized by several reporting systems. Thus, the incorporation of a separate category for these patients in the 2023 FIGO (new stage IA3) is, in principle, well-received. However, the criteria to define this subset are not uniformly established in the literature. For instance, bilateral ovarian involvement by tumor is a criterion of unfavorable outcome in the 2023 FIGO, ICCR, and ISGyP Endometrial Cancer Project recommendations, but not in the 2020 WHO classification. Similarly, LVI qualifiers (focal vs substantial) are used by 2023 FIGO and WHO but not by ICCR and ISGyP recommendations. Precursors to endometrioid carcinoma in the endometrium (atypical hyperplasia) and in the ovary (endometriosis, adenofibroma) are among the criteria for classification of favorable outcome by ICCR and ISGyP recommendations, but not WHO or 2023 FIGO. The 2023 FIGO update fails to provide evidence in favor of their approach rather than the approach used in other recommendations.

Regarding the incorporation of molecular results in FIGO 2023 staging, we offer several points for consideration. First, the incorporation of molecular parameters essentially precludes staging as proposed in resource-poor settings. Second, the methodology for determining the molecular group is not specified in the 2023 FIGO update, which carries potential deleterious implications because of variation in testing for TP53 and MMR abnormalities and POLE mutations. A combination of immunohistochemistry and standalone POLE sequencing appears to be the preferred approach based on the current evidence. However, these ancillary tools have great variability in terms of access, workflow, interpretation, and reporting. DNA sequencing assays suffer from long turnaround times, and the pathologist may find the workflow related to ancillary testing and optimal incorporation into the pathology report challenging. Lastly, as POLE testing has become more widespread, assays have expanded from limited ‘hot spot’ sequencing of POLE to full exonic sequencing within targeted next generation sequencing panels. This has created great opportunities to learn more about the effects of specific POLE mutations, but has also led to the identification of variants of unknown significance. Given the significant changes in stage and clinical management imparted by POLE status alone, clear direction as to which pathogenic POLE mutations are appropriate to classify an endometrial cancer as ‘POLEmut’ is essential.

Unnecessary Duplication of Risk Stratification Models

The 2023 FIGO staging system resembles the approach taken by 2021 ESGO/ESTRO/ESP guidelines in defining risk categories based on multiple pathological features beyond anatomic spread. In fact, the authors of the FIGO 2023 system state that the ESGO/ESTRO/ESP guidelines were used as a template. Whether the stage should be an element of patient risk stratification models or become the risk model itself by incorporating other factors beyond anatomic tumor extent is still debatable. However, we argue that ‘refining’ stage as the overarching and all-inclusive cancer stratifier has important drawbacks. Staging as traditionally conceived is a concept familiar to all cancer care providers; it is practical and applicable in under-resourced settings where the capacity to perform ancillary studies may not exist and the FIGO staging update is difficult to apply on a global scale.

Less Applicability and Adoption by Stakeholders

Another significant drawback is related to the considerable variability worldwide in terms of access to diagnostic and therapeutic modalities. There have been considerable advances in endometrial carcinoma classification, transitioning from an era of poor reproducibility in histologic typing and grading to a more objective and reproducible molecular classification, although with the caveats regarding POLE, TP53, and MMR testing discussed earlier. Patients are increasingly knowledgeable about the concept of personalized medicine, and that their care may differ from other patients based on molecular features, ranging from de-escalation of therapy to targeted treatments. Clinical trials that have stratified treatment assignment by molecular features have high patient acceptance rates.

For treating clinicians, international multidisciplinary efforts for undertaking molecular testing by the WHO, ESGO/ESTRO/ESP, ICCR, and other bodies have, in our opinion, successfully driven change globally. However, a wide variability in implementation exists. Some of this variation is driven by the resources available, and some by knowledge translation and education. Allowing clinicians to maintain their traditional practice of assigning stage based on anatomic spread of disease, but allowing them to include molecular features and other non-anatomic parameters for clinical context and decision making, has been successful in generating impactful change in endometrial carcinoma management; there are concerns that a one-time set of changes across the entire staging system as proposed by FIGO may impede this progress.

There is significant concern that the new FIGO staging system will confuse both patients and clinicians. It will potentially frustrate those who are only recently coming to terms with the value added by molecular subtyping. It may pose even greater challenges to those who lack the tools (molecular testing, immunohistochemistry) to implement the staging system as proposed; to them, the most critical piece of the puzzle in their cancer care will be missing. The system also creates an extra step of memorizing a new non-anatomic staging system that is non-intuitive. In discussing a historical clinical trial with a patient, extensive explanation of stage differences will be required, and it is unlikely that interpretation of treatment efficacy will be possible. For new or currently active clinical trials, it is unclear how enrolment criteria could be adapted to fit the new FIGO system. It is also possible that disparities in clinical trial enrolment between institutions could be exacerbated.

Further, we anticipate confusion with the assigned stage potentially changing at different points during the patient’s cancer journey. For example, a hysterectomy specimen deemed to have a grade 2 endometrioid carcinoma with invasion into the outer half of the myometrium (stage IB), is reviewed at a local cancer center where the tumor is considered grade 3, and therefore assigned FIGO stage IIC; finally, when molecular classification results become available and a pathogenic POLE mutation is identified, the same patient has the stage changed to stage IAm."POLEmut".

Lack of Supporting Evidence

Added to the lack of a detailed description regarding evidence appraisal methodology, of concern is the fact that many of the
changes and recommendations are provided without any citations. Throughout the text, the 2023 FIGO update lacks references to original, peer-reviewed literature in support of many of the proposed changes. For instance, the publication does not provide recent evidence supporting the re-introduction of evaluating superficial myometrial invasion versus no myoinvasion, or the grouping of FIGO grade 3 endometrioid carcinoma, a molecularly and clinically heterogeneous group, with other histologic subtypes as ‘aggressive’ histologic carcinoma types. Where there is discordance in heterogeneous group, with other histologic subtypes as ‘aggressive’ histologic carcinoma types. Where there is discordance in heterogeneous group, with other histologic subtypes as ‘aggressive’ histologic carcinoma types. Where there is discordance in heterogeneous group, with other histologic subtypes as ‘aggressive’ histologic carcinoma types. 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We express concern that the recent FIGO staging update lacked the rigorous process that is expected for the magnitude of its recommendations. The authors of the FIGO update state that they have performed a literature review but do not provide any further details on the process. The methodology section does not mention any feedback rounds, external review, or opportunities for input by relevant gynecology, pathology, gynecologic oncology, medical oncology, and radiation oncology societies. There is also no mention of a public consultation period, in which the proposed changes are subjected to the review of the medical and scientific community at large. Given the scope and significance of the changes, we are of the opinion that substantial input by the ISGyP and other relevant societies should have been sought prior to publication of the update. An open comment period would have also been greatly beneficial and likely to increase adoption.

Importantly, the limited pathology input in the FIGO 2023 endometrial carcinoma update follows an unsettling trend by FIGO of limiting and/or omitting pathologist’s input in their staging recommendations, as evidenced by the most recent updates for carcinomas of the uterine cervix and vulva. In fact, FIGO did not include a single gynecological pathologist in either of these publications. Expectedly, this has resulted in issues that have caused major confusion in the field, increasing heterogeneity among practices, and likely leading to disparities in patient care. If FIGO intends to retain the confidence of pathologists and other clinicians, the issues highlighted herein need to be rectified.

In 2021, the ISGyP carried out a survey among pathologists and treating clinicians to identify and rank perceived controversies in endometrial carcinoma staging as well as areas lacking solid evidence, with the overarching aim of defining topics for future outcome-based research to inform subsequent changes in the staging system. The survey was circulated via email to members of the ISGyP and the International Gynecologic Cancer Society and drew responses from 172 pathologists and 135 treating clinicians. We acknowledge that the 2023 FIGO update addresses many of the relevant points covered in the survey. Notably, however, very few questions elicited a consensus response, defined as at least 75% agreement among either pathologists or treating clinicians. Those that approached or reached consensus have in fact been addressed in the 2023 FIGO update: substaging of nodal involvement based on the size of metastasis, defining criteria to separate cases of simultaneous uterine corpus and ovarian carcinoma into favorable versus unfavorable prognostic categories, and agreement that LVSI represents an independent prognostic variable.

Conversely, additional changes in the 2023 FIGO update did not achieve consensus agreement among pathologists or treating clinicians. A slim majority of pathologists (52%) and a higher proportion of treating clinicians (65%) supported the incorporation of histological tumor type into staging. Likewise, 48% of pathologists and 61% of treating clinicians agreed that LVSI should be incorporated into staging. Regarding LVSI, defining the cut-off between focal and substantial LVSI was identified as the leading research priority. Finally, 48% of pathologists and 63% of treating clinicians felt that molecular classification should be incorporated into staging.

What To Do Now and in the Future?

As outlined in this appraisal, there are both advantages and drawbacks with the new FIGO staging system for endometrial carcinoma. A healthy dialog regarding the staging system is warranted before adoption and implementation, and alternatives can be devised to address its shortcomings. The introduction of parameters beyond anatomic distribution of disease could be addressed by retaining the FIGO 2009 staging system or modifying it slightly with supplementation of prognostic data as modular units appended to the original stage; this approach would allow for incorporation of prognostic information where available, which is an important factor to consider as staging systems are employed worldwide and in areas without access to molecular testing. Other potential options, such as devising a staging system for each of the four molecular categories, could be considered but, like the updated FIGO system, would be complicated and difficult to apply.

As outlined above, the lack of substantial representation of the pathology community (as well as other stakeholders including patients and general gynecologists) on the FIGO Women’s Cancer Committee is a major deficiency. Staging systems, and other parameters needed for patient prognostication and to guide management, rely heavily on pathology parameters. It is therefore logical that development and update of such systems fundamentally requires sufficient and timely pathology input. The pathology community should not only be informed but be fully engaged in guiding any significant changes.
The new FIGO staging system should be first appraised at a multi-institutional and global level with the input of all stakeholders to understand the impact and scope of the proposed changes and whether clinicians and pathologists wish to embrace it. Identification of supporting evidence (or lack thereof) is also required before adoption. In the meantime, anatomic staging is more universally applicable and easier to integrate with other variables relevant to risk assessment in concert with the local resources. Regional and national guidelines for risk stratification, such as ESGO/ESTRO/ESP and NCCN, are more likely to achieve such integration successfully. A universal guide for risk assessment would of course be ideal, but it would require homogeneity in diagnostic and therapeutic resources worldwide. Since that is unlikely to exist in the foreseeable future, a blanket approach like the one proposed by the 2023 FIGO is more likely to create significant gaps in cancer care between resource-rich and resource-poor healthcare systems, further deviating from the goal of ‘personalized’ medicine.

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