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Review

Controversies in the Management of Early-stage Serous Endometrial Cancer

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Abstract. *Background/Aim: Early-stage uterine serous carcinoma (USC) has one of the highest recurrence rates and mortality among early-stage uterine epithelial cancers. Research into the clinical management of USC has begun to progress, guided by surgical and pathological advances. This article summarizes the available literature regarding diagnosis, management, and possible future uses of molecular analysis of women with early-stage USC. Materials and Methods: PubMed was searched for all pertinent English language research articles published from January 1, 2006 through March 1, 2020 which included a study population of women diagnosed with stage 1 USC. Due to the scarcity of prospective or large-scale data, studies were not limited by design or numbers of patients. Studies performed at earlier dates were incorporated to provide context. Results: A total of 86 studies were included in the review. Multiple well-designed studies have confirmed the safety of a minimally invasive surgical approach for surgical management of USC. The role of sentinel node biopsy has been validated with both prospective and retrospective multi-center data. Stage I USC is associated with a highly variable risk of recurrence, even following completion of adjuvant chemoradiation. This aggressive phenotype has been linked to high numbers of somatic copy number alterations, tumor protein 53, and phosphatidylinositol 3 kinase mutations, which have been shown to be predictive of prognosis. Conclusion: Early-stage USC demonstrates a lack of predictable recurrence patterns, with reports noting distant recurrence in patients with disease confined to polyps. Unless no residual tumor is found on hysterectomy, chemotherapy and radiotherapy should be discussed and individualized by stage and treatment goals.*

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High-grade uterine serous carcinoma (USC) has an aggressive natural history, and relatively poor prognosis in contrast to its endometrioid counterparts (1). Stage I USC is a rare tumor which represents a unique combination of higher risk histology and lower risk stage. Current literature reports highly variable recurrence rates and inconsistent recommendations for adjuvant treatment (2-4). Accurate surgical staging is paramount to guiding treatment and informing prognosis, and includes hysterectomy, bilateral salpingo-oophorectomy, lymph node assessment, and omental biopsy (5).

Recent advances have been made in the molecular classification of uterine carcinomas. This testing has been able to identify aggressive alterations in patients with low-grade endometrioid histology. In contrast, molecular alterations associated with favorable prognosis have been identified in patients with higher grade or high-risk histology (6). As this information accumulates, it will start shaping our clinical decisions for adjuvant treatment and patient counseling. In this review, we discuss the current treatment strategies of early-stage USC and outline possible applications of molecular classification in the treatment of this disease.

Materials and Methods

PubMed was searched for all English language research articles published from January 1, 2006 through March 1, 2020 which included the study population of women diagnosed with early-stage (stage 1) USC. Key words included "serous endometrial" and "serous uterine", which yielded 1,848 eligible articles. These were filtered by relevancy to the topic and applicability to clinical practice or molecular analysis. The resultant article bibliographies were cross-referenced to identify further publications for inclusion. Due to the scarcity of large-scale prospective data, studies were not limited by design or numbers of patients. Preference was given to meta-analyses, prospective studies and clinical trials when applicable. Non-translational basic science studies were excluded (n=640). This design is summarized in Figure 1.

Results

Epidemiology. Risk factors for USC include advanced age and African American race. At present, over 22% of cancer cases in women over 70 years of age are serous histology, compared with only 3% of women less than 45 years old (7).

Additionally, African American race may have an increased incidence of USC, a finding which was first noted in a Gynecologic Oncology Group (GOG) sub-analysis (8). In this study, 39% of African American women had high-grade serous endometrial cancer compared to 16% of Caucasian woman. This disparity appears to be more pronounced among older rather than younger African American women (9, 10). This finding may partially explain the racial disparities noted in survival outcomes of patients with endometrial cancer but caution should be given to interpretation of these results due to multiple confounding variables (11).

The presence of pre-disposing germline cancer mutations has been found in 6.7% of all patients with USC, an incidence which is higher than for other histological subtypes (12, 13). In 2016, Shu *et al*. reviewed the incidence of serous endometrial carcinoma after risk-reducing salpingo-oophorectomy in 1,083 women with germline Breast Cancer Gene (*BRCA)* mutations, and noted four cases in 627 patients with *BRCA1* mutation. The rate of USC in this group was 22.2-fold greater than expected. Limitations in their study included the small number of cases, and use of tamoxifen in three out of these four patients (14). In 2019, Long *et al*. expanded upon these findings by reviewing germline mutation incidence in a large cohort of patients with endometrial cancer, including 135 with serous histology. They noted the presence of germline mutations, including 1.48% BRCA1-interacting protein *C*-terminal helicase (*BRIP1)*, and 0.74% each of ataxia telangiectasia mutated (*ATM), BRCA1,* MutS homolog 6 *(MSH6),* neurofibromin *(NF1),* PMS homolog 2 *(PMS2)*, and tumor protein 53 (*TP53)* in patients with serous histology (13). Given the risk of germline mutation, a comprehensive family history should be obtained in the clinical setting, and consideration given to referral for genetic testing.

Initial diagnosis. Consistent with other histologies of endometrial cancer, women with USC often present with vaginal bleeding. Initial evaluation often includes pelvic ultrasound in an attempt to limit the need for invasive biopsy. Clinical guidelines have determined that office clinical biopsy can be safely omitted in patients with an endometrial complex thickness of <5 mm (15). However, these guidelines were predominately based on studies validating the negative predictive value of a thin stripe on tumors with endometrioid histology. Unfortunately, a significant proportion of USCs may be missed using these criteria, as they more commonly present with a thin endometrial stripe (16-18). Additionally, concerns have been raised regarding the sensitivity of office endometrial biopsy on patients with endometrial stripe thickness <5 mm as the ability to produce a sufficient diagnostic sample is limited, with numbers as low as 27% reported in the literature (19).

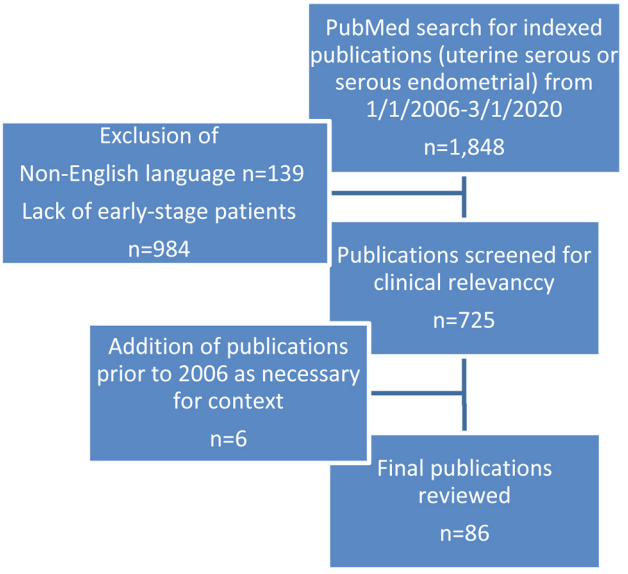

Figure 1. *Study design of literature review.*

The pre-operative serum level of cancer antigen 125 (CA-125) has been advocated as a biomarker for extra-uterine disease and prognosis, similarly to its use in serous epithelial ovarian carcinoma. A recent study by Schmidt *et al*. observed that high CA-125 levels correlated with positive cytology, omental, nodal, or adnexal disease (20). They found the traditional cutoff of 35 U/ml to have a sensitivity of 80% and specificity of 76% for predicting extra-uterine disease, and advocated a new threshold of 41 U/ml to increase specificity. Debate remains as to whether CA-125 is an independent predictor of survival in these patients, with conflicting evidence to date (21-24).

Surgical approaches. Comprehensive surgical staging in patients with serous endometrial cancer is paramount as 37-39.4% of patients without myometrial invasion on hysterectomy have been found to have extra-uterine disease upon complete staging (25, 26).

Both large-scale prospective and retrospective data have shown a minimally invasive surgical approach to be safe for patients with early-stage serous uterine disease (27, 28). The well-known LAP2 trial compared disease-free and overall survival following randomization to abdominal or laparoscopic hysterectomy in 679 patients with stage 1 endometrial cancer. This study included patients with serous histology in 12% of the abdominal hysterectomy and 7% of laparoscopic hysterectomy groups, and noted equivalency in

recurrence rates and overall survival (27). Stemming from this trial, several sub-analysis studies were performed in specific patient groups. In their sub-analysis of patients >60 years of age, Bishop *et al*. noted reduced postoperative complication and morbidity scores among those who underwent minimally invasive surgery, a finding of particular importance to the older cohort of patients with serous cancer (29). Fader *et al*. performed a sub-analysis of the patients with high-grade histology, including 289 with USC, finding no changes in recurrence or survival by surgical approach (30). Minimally invasive approaches have now become utilized as a quality measure in high-volume National Cancer Care Network (NCCN) centers (31-33). Indeed, the adoption of these approaches in the past 10 years has resulted in large improvements in all-cause operative and postoperative morbidity (32).

The performance of full lymphadenectomy as part of comprehensive staging of endometrial cancers has declined in response to the ASTEC trial, which did not demonstrate a survival advantage to systematic pelvic and para-aortic lymphadenectomy (34). Serious morbidity is associated with full lymphadenectomy, including increased intraoperative bleeding, nerve injury, lymphocele, infection, prolonged hospital stay and lymphedema (35). Additional studies have demonstrated that systematic lymphadenectomy does not improve survival in endometrial cancer but does increase surgical morbidity (36). Sentinel node biopsy has been shown to reduce the risk of surgical morbidity (37, 38), and was recently endorsed by the Society for Gynecologic Oncology and NCCN as a reasonable alternative for surgical staging (39). In response, centers have developed protocols for the use of sentinel lymph node biopsy based on risk factors, leading to worldwide variability in practice (40). Recent publications have shown that sentinel lymph node biopsy with ultrastaging detects a high percentage of metastasis in patients with high-risk endometrial cancer (41, 42). Prospective data were obtained in the FIRES trial (43), which enrolled N=41 (12%) of patients with serous histology for sentinel node biopsy followed by completion pelvic and peri-aortic lymphadenectomy. The study was able to affirm the high degree of diagnostic accuracy in detecting endometrial cancer metastases, and asserted that this practice can safely replace lymphadenectomy in the staging of endometrial cancer. Clinically, this information supports the use of sentinel node biopsy in routine surgical management of patients with early-stage serous endometrial cancer. Baiocchi *et al*. randomized 236 women with high-grade endometrial cancer and normal-appearing nodes on preoperative computed tomography to sentinel lymph node biopsy and completion lymphadenectomy or full lymphadenectomy. Interestingly, more pelvic lymph node metastases were observed in the sentinel node group than the lymphadenectomy group (26.7 *vs*. 14.3%; p=0.02). They also did not identify any peri-aortic metastasis in women with mapped sentinel lymph nodes (41). Touhami *et al*. examined the practice of sentinel node biopsy followed by completion lymphadenectomy in 128 patients with high-grade endometrial cancer, finding a 63.2% bilateral detection rate, with 95.8% sensitivity and 98.2% specificity (44). Additionally, Naourae *et al*. examined the impact of ultra-staging of sentinel nodes on detection of nodal metastasis in 180 patients with presumed early-stage high-risk endometrial cancer. Ultra-staging detected metastases undiagnosed by conventional histology in 41% of patients with node-positive disease, with a low false-negative rate of 6% (42). The use of sentinel node algorithms in patients with USC has been tested in large multi-center studies which confirm a high sensitivity for nodal metastasis (45), without compromise in overall survival (46, 47).

With the use of sentinel node biopsy, circumstances may arise where omission of peri-aortic lymph node assessment might be considered. Previous studies without the use of sentinel node biopsy and ultrastaging found the incidence of isolated peri-aortic metastasis in high-grade non-endometrioid histology to be around 5% in the absence of gross extra-uterine disease and deep myometrial invasion (48). This rate may potentially be even lower in patients with ultrastaging of the pelvic lymph nodes (49). In two newer trials, by Rossi *et al*. (43) and Soliman *et al*. (45), in which 41 and 30 patients with USC, respectively, were noted to have no incidence of isolated peri-aortic metastasis in cases of adequate mapping and negative pelvic sentinel lymph nodes. While patients with USC were included in these studies, their numbers are limited relative to those with other histological subtypes, and further study is needed. If omission of peri-aortic lymph node assessment is considered, confirmation of normal nodal architecture and absence of gross intra-peritoneal disease on preoperative computed tomography is suggested by some institutions (46).

The procedure of sentinel node biopsy is not affected by serous histology. Traditionally, a dye (blue-based, or indocyanine green) is injected into either the uterine fundus or cervix, with the latter becoming more common due to the increase in minimally invasive surgery, the demonstration of higher overall detection rates, and NCCN endorsement (35, 50). Indocyanine green has the highest bilateral detection rate and an overall detection rate of >96% (51-53).

Other staging considerations include omental biopsy and the performance of peritoneal cytology. Omental biopsy has been advocated to be included in comprehensive staging as it can dramatically upstage and inform prognosis for patients. Omental metastasis is seen in 6.5-25% of patients with a grossly normal appearing omentum at the time of surgery (54, 55). Fortunately, this practice has been shown to be safely completed *via* a minimally invasive approach (55).

Peritoneal cytology, while removed from staging in 2009, may provide additional prognostic and research information at no additional surgical risk to the patient (56).

Pathologic and molecular analysis. An important question remains for patients with early-stage endometrial cancer: What pathological and genomic/molecular features, if any, are predictive of future disease progression? While variables such as tumor diameter, linear extent of myometrial invasion, percentage myometrial invasion, lymphovascular space invasion, and percentage serous histology have all been analyzed in small studies, none has achieved reproducible prognostic utility, specifically for early-stage serous tumors (57-62). Only the presence of *any* degree of myometrial invasion has been found to confer a non-significant trend in many small studies towards an increased risk of recurrence (63, 64).

With the recent completion of The Cancer Genome Atlas, endometrial cancer has been classified into four subcategories which have been found to be predictive of prognosis (6, 65-68). In tumors with serous histology, alterations within the high somatic copy number alteration (SCNA) subcategory are most common (in 97.7% of serous tumors), in contrast to the copy number-low/phosphatase and tensin homolog deleted on chromosome 10 (*PTEN)* -mutated, polymerase-epsilon (*POLE*) ultra-mutated, and mismatch repair-deficient tumors, which typically have endometrioid histology. The extent of SCNA has been found to correlate negatively with progression-free survival (6).

Clinically, how do we anticipate this testing affecting future patient care for patients with early-stage USC? The answer to this question is multi-dimensional and complex. Firstly, we know that histology is not always predictive of tumor behavior, and that tumor histological phenotype does not always perfectly correlate with genotype. For example, Kandoth *et al*. found 5% of tumors with grade 1-2 endometrioid, and 24% of tumors with grade 3 endometrioid histology had SCNA "serous-like" mutations, and that these may behave more aggressively (6). Adjuvant therapy for a stage IA, grade 3, endometrioid tumors is often limited to vaginal brachytherapy. However, if this same early-stage patient with deceptive high-grade endometrioid histology were to be diagnosed with genetically "serous type" high SCNA tumor, a more aggressive treatment may be recommended. Consideration may be given to treating these patients with high SCNA with chemotherapy, external beam radiotherapy, or a combination, given the correlation with poor progression-free survival.

Next, specific alterations within each subcategory may represent areas for current and future drug targeting. For example, among serous endometrial tumors, *TP53* is mutated in 90.7%, phosphatidylinositol 3 kinase (*PIK3CA)* in 41.9%, F-box and WD repeat domain containing 7 (*FBXW7)* in 30.2%, and human epidermal growth factor receptor 2 (*HER2)* in 30% (6, 69-72). These mutations are potential drug targets with either investigational or currently available targeted therapies (70). Although more data are needed in patients with early-stage disease, current data are promising at extending the progression-free survival interval in patients with more advanced-stage serous histology *via* the addition of commercially available targeted treatments to the standard of care chemotherapeutics (69, 73). Notable among these, Fader *et al*. recently completed a phase II trial in patients with advanced-stage or recurrent disease, which demonstrated an increase in progression-free survival by over 4 months with the addition of trastuzumab to the standard of care carboplatin-paclitaxel chemotherapy in HER2-overexpressing USC (69). Further study is needed to confirm the benefits of additional targeted therapies specifically in those with early-stage disease, who have been hypothesized to receive less benefit than their advanced-stage counterparts (69).

Lastly, genomic and molecular analyses may predict response to specific chemotherapeutics. While platinum-based chemotherapy remains the mainstay, other agents may be used at recurrence with refractory or resistant disease (69). Multi-omic testing in this setting may guide therapy. For example, detection of low-density lipoprotein receptor-related protein 1B (*LRP1B)* deletions has been shown to be associated with doxorubicin resistance in other serous tumor types (74).

Taking these findings into consideration, the future direction of analysis may shift to testing for the categories as defined by The Cancer Genome Atlas (POLE, mismatch repair deficient, and T53/SCNA), which might be of particular utility in cases with ambiguous histology (6). At the time of a recurrence, new tissue samples may be obtained and consideration should be given to expanded testing for targeted mutations with commercially available treatments (*e.g. HER2* and somatic *BRCA*) to individualize treatment decisions.

Adjuvant chemotherapy and radiotherapy. Outside of surgery, the ideal adjuvant management of stage IA USC remains highly controversial (75, 76). Initial adjuvant chemotherapy for USC has been extrapolated from platinum-based chemotherapeutic regimens used to treat high-grade serous ovarian carcinoma. NCCN guidelines at present suggest that post-surgical treatments can include observation, adjuvant chemotherapy, vaginal brachytherapy, external beam radiation, or any combination of the above (50). The field has resorted to applying proven therapies for more advanced-stage disease to early-stage disease, in the hope of achieving a benefit.

The impact of platinum-based regimens on overall and failure-free survival was recently demonstrated in the PORTEC-3 trial, in which 105 patients with all stages of USC received either radiotherapy or combination chemoradiotherapy (3). The addition of platinum-based chemotherapy increased failure-free survival for patients with serous endometrial carcinoma from 47.9% to 59.7% over 5 years. One notable concern is that while patients were analyzed by histology and stage separately, no sub-analysis of patients with early-stage serous cancer was possible due to limited numbers.

In 2013, Fader *et al*. completed a retrospective review of 11 studies to examine the role of adjuvant treatment on recurrence rates specifically in patients with early USC. In

Table I. *Approaches to management of early-stage serous endometrial cancer.*

Pathology	Mayo Clinic	GOG-249 (90)*	PORTEC-3 (3)**
No residual tumor in hysterectomy, negative peritoneal cytology	Observe	EBRT	EBRT + chemotherapy
Stage IA - No myometrial invasion, confined to a polyp	VB Discuss possible chemotherapy		
Stage IA - With myometrial invasion or positive peritoneal cytology	VB Suggest chemotherapy		
Stage IB	VB Chemotherapy		
Stage II Chemotherapy + EBRT	VB		

VB: Vaginal brachytherapy; EBRT: external beam radiation. *Comparing early-stage, high-risk endometrial cancer (15% serous) *vs*. VB + chemotherapy, found increased hazard ratio for pelvic or peri - aortic nodal recurrence in VB + chemotherapy at 3 years; no difference in overall survival was noted in subgroup analysis of patients with stage I serous disease. **Compared with EBRT alone in women with high-risk endometrial cancer, finding increased progression-free and overall survival with the addition of chemotherapy. Due to lack of statistical power, it was not possible to analyze survival stratified by stage in serous cancer.

patients with stage IA disease, they noted a trend towards reduced recurrence rates with adjuvant chemoradiotherapy (7/86, 8.1%) compared to observation (18/145, 12.4%) or radiation (10/50, 25%) but this did not reach significance, nor did it explain the heightened recurrence rate in the group those with radiation alone (1).

With the addition of platinum-based therapies to nearly all stages of USC following PORTEC-3, and the possible but yet largely unproven benefit in some patients with earliest stage IA disease (1, 77, 78), we anticipate it becoming even more difficult to determine the effect of this practice migration to near universal adjuvant chemotherapy administration from clinical data alone. Barriers to finding this answer include a limited number of patients with early-stage USC, the high number needed to treat to obtain a survival benefit, and limited numbers of patients undergoing observation.

The role of radiation in patients with early-stage disease has been analyzed *via* meta-analysis. Lin *et al*. demonstrated a progression-free survival benefit of adding radiation to chemotherapy when analyzing 9,354 patients from multiple national cancer registries, an effect that persisted when adjusting for early-stage disease (2).

Both retrospective and prospective studies have found a benefit of combination chemotherapy and vaginal brachytherapy in a small number of patients with IA disease but the sample size and inconsistent staging practices limit definitive generalizability (61, 78-86). In contrast, other retrospective studies failed to show a survival benefit with the addition of platinum-based chemotherapy to vaginal brachytherapy for patients with early-stage, high-risk cancer (87). To address this disparity, Qu *et al*. performed a recent comprehensive analysis of all IA serous cases at six high-volume cancer centers, finding increased regional control in patients treated with combination adjuvant chemotherapy and radiation (64). Interestingly, others noted that this benefit did not apply in patients undergoing lymphadenectomy (63), which represented fewer than 25% of patients in Qu *et al*.'s study.

Challenging clinical decision making arises when confronted with a patient with serous histology on preoperative biopsy but no residual disease on hysterectomy, or disease confined to a polyp. Hui *et al*. reviewed the outcomes of 22 patients with disease confined to a polyp, or without residual disease within the uterus, and saw no recurrences after a median follow-up of 26 months (range=0-67 months) (88). Conversely, reports of distant and unsalvageable recurrences in such patients have been published (82), including well-staged patients with disease confined to a polyp who received chemoradiotherapy (89). In this setting, we suggest counseling the patient regarding the role of chemotherapy in more advanced stage disease, and the limited evidence in their individual setting, and arriving at patient-centered individualized treatment decisions together. Our treatment paradigm for patients with early-stage USC is summarized in Table I, and is contrasted with the approaches suggested by GOG-249 (90), and PORTEC-3 (3).

Recurrence patterns. Unfortunately, recurrence risk estimates on stage 1 USC vary widely in the literature, ranging from 0-70% of patients with IA disease, with most estimates centering between 10% and 25% (30, 78). This recurrence is often systemic [50% of patients in one study (4)], and potentially unsalvageable. Indeed, recurrences have even been noted in small numbers (9%) of well-staged patients with disease confined to a polyp (82), and in up to 30% of those without any myometrial invasion (5, 77, 82).

Given this unpredictability, even patients with stage IA or non-invasive disease should be followed closely in the postoperative period, in accordance with NCCN guidelines.

The role of CA-125 in the detection of recurrence in patients with early-stage USC has yet to be demonstrated but could be considered on an individualized basis (24).

Discussion

Early-stage USC represents a rare tumor with a high risk of recurrence between 10-25%. USC is best staged using a minimally invasive surgical approach. Surgical staging includes hysterectomy, bilateral salpingo-oophorectomy, lymph node assessment and omental biopsy. Sentinel node biopsy is becoming the favored approach for nodal assessment in endometrial cancer and emerging data has demonstrated the validity of this approach in USC.

Currently, there is no consensus on the ideal adjuvant treatment for patients with early-stage USC. The available literature demonstrates a high risk of recurrence even in well-staged patients with stage IA, with the majority of recurrences exhibiting distant or non-localized spread. Adjuvant therapy options include chemotherapy, vaginal brachytherapy and external beam radiation therapy. It does appear that some patients with early-stage USC, such as those with disease confined to a polyp, have a low risk of recurrence and thus an individualized approach with less aggressive treatment or observation can be discussed with the patient. Further prospective studies are needed to clarify the ideal approach to adjuvant treatment in these patients.

Molecular analysis has reliably subcategorized endometrial cancers into four molecular types. USC is associated with SCNA, *TP53* and *PIK3CA* mutations which are in turn predictive of poor prognosis. Molecular analysis is helpful in cases with ambiguous histology and should be considered in this context. At the time of writing, molecular classification has not further stratified patients with early-stage USC to better predict which are likely to experience recurrence. Additional analysis is needed to determine if molecular classification can better tailor adjuvant therapy for our patients. Lastly, at the time of recurrence, novel targeted treatments currently appear promising in extending progression-free survival. Therefore, consideration should be given to testing for *HER2* and somatic *BRCA* alterations.

Given these recent advances, and the remaining uncertainties, we propose closely tracking the outcomes of these patients at each institution, and considering multi-institutional collaborations so that we may continue to optimize surgical and adjuvant treatments. Future areas of research should focus on delineating which patients with early-stage USC are most likely to benefit from adjuvant therapy and on developing targeted therapies for treatment of recurrences.

Conflicts of Interest

All Authors report no conflicts of interest.

Authors' Contributions

All Authors contributed meaningfully to the creation of this work.

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