# Active surveillance for the management of localized prostate cancer: Guideline recommendations

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## Abstract

**Introduction:** The objective is to provide guidance on the role of active surveillance (AS) as a management strategy for low-risk prostate cancer patients and to ensure that AS is offered to appropriate patients assessed by a standardized protocol. Prostate cancer is often a slowly progressive or sometimes non-progressive indolent disease diagnosed at an early stage with localized tumours that are unlikely to cause morbidity or death. Standard active treatments for prostate cancer include radiotherapy (RT) or radical prostatectomy (RP), but the harms from over diagnosis and overtreatment are of a significant concern. AS is increasingly being considered as a management strategy to avoid or delay the potential harms caused by unnecessary radical treatment.

**Methods**: A literature search of MEDLINE, EMBASE, the Cochrane library, guideline databases and relevant meeting proceedings was performed and a systematic review of identified evidence was synthesized to make recommendations relating to the role of AS in the management of localized prostate cancer.

**Results:** No exiting guidelines or reviews were suitable for use in the synthesis of evidence for the recommendations, but 59 reports of primary studies were identified. Due to studies being either non-comparative or heterogeneous, pooled meta-analyses were not conducted.

**Conclusion**: The working group concluded that for patients with low-risk (Gleason score ≤6) localized prostate cancer, AS is the preferred disease management strategy. Active treatment (RP or RT) is appropriate for patients with intermediate-risk (Gleason score 7) localized prostate cancer. For select patients with low-volume Gleason 3+4=7 localized prostate cancer, AS can be considered.

## Introduction

Prostate cancer is often a slowly progressive or non-progressive indolent disease diagnosed at an early stage with localized tumours that are unlikely to cause morbidity or death.[1] Standard active treatments for prostate cancer include radiotherapy (RT) or radical prostatectomy (RP). However, harms from overdiagnosis and overtreatment are a significant concern and the risks of active treatment may outweigh the benefits in many patients, particularly those with low-grade disease. To address these concerns, AS is increasingly being considered as a management strategy to avoid or delay the potential harm caused by unnecessary radical treatment[2] in those patients with prostate cancers that are unlikely to progress.

There are no published randomized controlled trials (RCTs) comparing AS to active interventions. Some of the evidence used in this guideline comes from trials comparing active intervention (such as RP) to watchful waiting or observation. AS differs from watchful waiting or observation in both intent and in the utilization of serial biopsy strategies. The intent of watchful waiting or observation is to avoid active intervention in patients with limited long-term survival expectancy by providing delayed non-curative therapy for patients who experience metastatic progression. Patients with Gleason ≤6 prostate cancer rarely experience metastatic progression on watchful waiting or observation and therefore the members of the Working Group and Expert Panel feel that the results from these trials give important natural history information and the results can be used to inform this guideline on AS.

The intent of active surveillance is curative, allowing the option of active treatment for those patients on AS who are reclassified to higher risk or who show disease progression. Active surveillance involves regular follow-up testing for prostate-specific antigen (PSA), digital rectal examination (DRE), repeat prostate biopsy, and use of prostate imaging,

when indicated. The goal of this strategy is to monitor cancers at low risk of future progression to select patients with occult cancers of higher grade and risk who require timely therapy, while maintaining surveillance on patients who remain classified as having low-risk cancers.[1]

Most prostate cancers at low risk of future progression are the low-grade cancers which have the most favourable outcomes. The Gleason grading system is effective in predicting the biological behaviour and prognosis of these cancers. In combination with measurements of tumour extent, Gleason score is the most meaningful pathologic determinant of eligibility for AS protocols. Modifications to the Gleason scoring system in recent years have enabled us to identify more homogeneous, truly low-grade Gleason <6 prostate cancers.[3] Pure Gleason 6 cancers defined according to these criteria showed lymph node metastases in only 0.48% of patients in a recent meta-analysis of 21 960 RP specimens.[4]

In Ontario, the selection of patients and the protocols used for AS vary across the province, and the importance of establishing a standardized protocol for AS has led to the development of these evidence-based recommendations. The term "low-risk" prostate cancer as used in this guideline is defined as the risk status for patients who have Gleason score ≤6, PSA <10, and ≤ stage T2A. The Working Group and Expert Panel defined the target populations for AS recommendations by Gleason score ≤6 and also Gleason score 3+4.

## Formation of the working group

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care. The CCO Surgical Oncology Program asked the PEBC to develop a guideline on active surveillance for the management of localised prostate cancer. In consultation with the Surgical Oncology Program, a Working Group was identified from Ontario. This Working Group consisted of two urologists, two pathologists, one radiation oncologist, and one methodologist. The Working Group and Surgical Oncology Program also formed the Active Surveillance Guideline Development Group whose responsibility is to provide feedback on the guideline as it was being developed and to act as an Expert Panel for the document at Internal Review.

### Objectives and research questions

The Working Group developed the following objectives for this guideline in consultation with the Surgical Oncology Program. The intention is to make recommendations that aim:

- To describe the role of AS as a management strategy for patients with localized prostate cancer
- To identify patients with prostate cancer that would most benefit from AS
- To develop an evidence-based protocol for AS in localized prostate cancer and identify the factors affecting the offer of, acceptance of, and adherence to active surveillance
- To understand the role of 5-alpha reductase inhibitors (5ARIs) (e.g., finasteride or dutasteride) in patients with localized prostate cancer undergoing AS
- To identify which physician is responsible for managing the active surveillance protocol and if any other human resources required to offer AS (e.g., a genitourinary pathologist, psychosocial specialist, etc.) would need specific training

From these objectives, the following research questions were derived to direct the search for available evidence.

1. How does AS compare with immediate active treatments (e.g., RP, RT, brachytherapy, hormone therapy, cryotherapy, or high-intensity focused ultrasound) as a management strategy for patients with newly-diagnosed localized prostate cancer (T1 and T2; Gleason score ≤7)?
2. In patients with localized prostate cancer undergoing AS, which findings of the following tests predict increasing risk of reclassification to a higher-risk disease state? What are their test characteristics (i.e., positive and negative predictive values, sensitivities, specificities, and likelihood ratios)?
   - PSA kinetics (e.g., velocity or doubling time)
   - DRE
   - Imaging (e.g., magnetic resonance imaging [MRI] or ultrasound [US])
   - Prostate cancer antigen3 (PCA3)
3. In patients with localized prostate cancer undergoing AS, how does supplementation with 5-alpha reductase inhibitors (5ARIs) (e.g., finasteride or dutasteride) compare with no supplementation?
4. In patients with localized prostate cancer undergoing AS, how do clinical outcomes differ if treatment is managed by a:
   - Single doctor versus a multidisciplinary team of clinicians?
   - Urologist versus another oncologist (e.g., a radiation oncologist)?
   - University/teaching hospital versus a community or private clinic/hospital?
5. In patients with localized prostate cancer who are candidates for or who are undergoing AS, how does the offer, receipt, or choice of treatment and patient compliance or adherence differ based on (but not limited to) the following factors:
   - AS protocol: order of and frequency of tests (PSA, DRE, imaging), and other test/clinical factors?

- Care provider(s): single versus team of doctors; urologist versus other oncologist?
- Care setting: clinic versus hospital?
- Patient factors: clinical, psychosocial?
- Social support: family or community?
- Socioeconomic or geographic variables?

## Methods

### Literature search strategy

Various guideline organizations and cancer agencies were searched for existing practice guidelines and systematic reviews on AS. MEDLINE and EMBASE databases were searched to identify studies published from 1996 to September 2013. The American Society of Clinical Oncology (ASCO) Annual Meeting, ASCO's Genitourinary Cancers Symposium, American Urological Association (AUA), European Association of Urology (EAU), Canadian Urological Association (CUA), and American Society for Radiation Oncology (ASTRO) proceedings from years 2010 to 2012 were also searched for relevant abstracts. Ongoing studies were identified by searching three online databases: clinicaltrials.gov, cancer.gov, and eortc.org.

### Study selection criteria

Practice guidelines, systematic reviews, RCTs, and other comparative studies were considered for inclusion. For conference abstracts, only RCTs reporting complete analyses were eligible for inclusion. For each research question, additional inclusion criteria were used. Studies on high-risk prostate cancer, cost-effectiveness, utility, and economics were excluded. Studies in languages other than English were also excluded due to lack of funding and resources for translation.

### Quality assessment and data extraction

Quality assessment of included studies was based on important quality features, such as study design, sample size, patient characteristics, length of follow-up, follow-up rate, support, and funding. For diagnostic study designs, additional quality features evaluated were gold standard, blinding, details of test administration, and outcomes. For RCTs, trial details and type of analysis, randomization method, statistical power, and blinding were also reported. Data from the included studies were independently extracted by one reviewer and all extracted data and information were audited by an independent auditor.

## Results

No existing guidelines or reviews from the environmental scan were suitable for incorporating into our guideline, but 57 full-text reports and 2 abstracts were retrieved from the primary literature search (Fig. 1). Due to studies being either non-comparative or heterogeneous, pooled meta-analyses were not conducted.

## Recommendation 1

**RECOMMENDATION 1:** For patients with low-risk (Gleason score ≤6) localized prostate cancer, AS is the preferred disease management strategy.

### Key evidence and qualifying statement for recommendation 1

High prostate cancer survival rates in several studies examining AS show that it is a reasonable management strategy for patients with low-risk (Gleason score ≤6) prostate cancer. Eight non-comparative studies of low-risk patients undergoing active surveillance reported prostate cancer survival rates of 100%[5-12] and another two non-comparative studies reported high prostate cancer survival rates of 97%[13] and

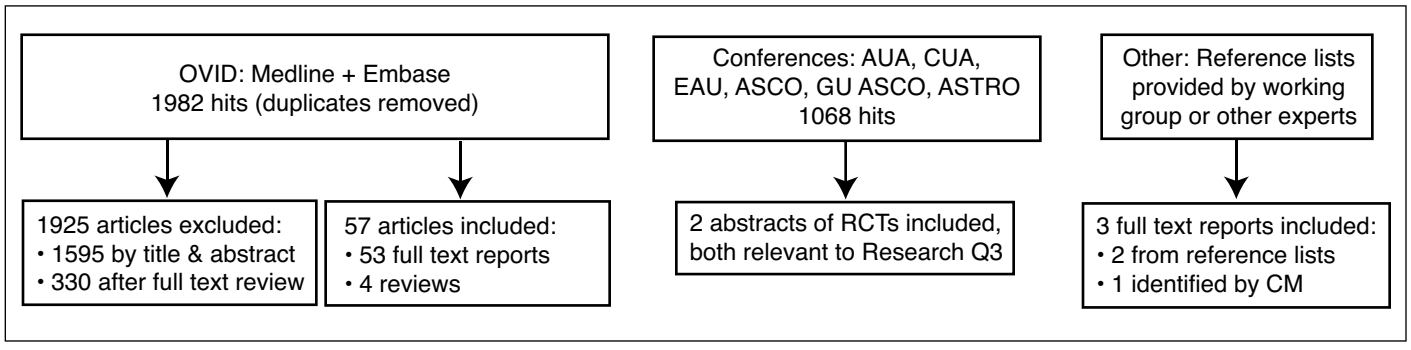


***Fig. 1.*** Schematic diagram showing results from the primary literature search.

98%, respectively.[14] Studies comparing immediate RP with delayed RP in patients undergoing AS detected no significant differences in biochemical recurrence rate, positive surgical margins, extraprostatic extension,[15-17] and risk of incurable cancer.[18-19] Clinical outcomes following immediate or delayed surgical treatment did not differ, suggesting that there is acceptably low risk associated with undergoing AS and delaying definitive therapy. The rate of harm due to adverse events from active treatments (RP, RT) is higher than with AS.

An RCT comparing RP with observation detected no significant difference between groups for prostate-cancer mortality rate and all-cause mortality rate after 12 years,[20] and the two most commonly reported adverse events associated with active surveillance (urinary incontinence and erectile dysfunction)[19-22] are similarly reported in other studies of immediate active treatments.[23-24] Therefore AS does not present any new or different harm. However, management options including active surveillance, RP and RT should only be undertaken after informed, shared decision-making consultations with the patient. It is known that there is heterogeneity within this population and therefore factors, such as younger age, high volume Gleason 6 cancer and patient preference, must be taken into account. Young patients (under 55) with high volume Gleason 6 cancer should be closely scrutinized for the presence of higher-grade cancer and definitive therapy may be warranted for select patients.

## Recommendation 2

**RECOMMENDATION 2:** Active treatment (RP or RT) is appropriate for patients with intermediate-risk (Gleason score 7) localized prostate cancer. For select patients with low-volume Gleason 3+4=7 localized prostate cancer, AS can be considered.

### Key evidence and qualifying statement for recommendation 2

In one non-comparative study of intermediate-risk patients undergoing AS, the prostate cancer survival rate was 100%.[25] In one non-randomized study comparing AS/watchful waiting versus RP versus RT, prostate cancer survival rates were similar at 95% versus 97% versus 96%, respectively.[14] An RCT comparing RP with observation detected no significant difference between groups for prostate-cancer mortality rate and all-cause mortality rate after 12 years, including intermediate-risk patients.[20]

Since prostate cancer survival rates in carefully selected intermediate-risk patients undergoing AS were similar to other active treatments, either active surveillance or active treatments can be recommended in this group of patients. Patients with Gleason score 7/10 (3+4) being considered for AS should include only those men with focal Gleason pattern 4 pathology, accounting for less than or equal to 10% total tumour. Due to known interobserver variability associated with the identification of minor Gleason pattern 4 elements, prospective intradepartmental consultation with colleagues should be considered a cornerstone of quality assurance in this area.[26,27] Pathologists should use uniform methodology when assessing and reporting the extent of cancer involvement in biopsy cores, especially when dealing with discontinuously involved cores[26] since volume and distribution of disease in prostate biopsies are also selection criteria for AS.

## Recommendation 3

**RECOMMENDATION 3:** The AS protocol should include the following tests:
- -PSA test every 3 to 6 months.
- -DRE every year.
- -12- to 14-core confirmatory transrectal ultrasound (TRUS) biopsy (including anterior directed cores) within 6 to 12 months, then serial biopsy a minimum of every 3 to 5 years thereafter.

The AS protocol may include the following test:
- -mpMRI is indicated when a patient's clinical findings are discordant with the pathologic findings and it is useful in identifying occult cancers or changes indicative of tumour progression in patients at risk.

### Key evidence and qualifying statement for recommendation 3

All AS protocol studies included in this guideline utilized a PSA test. Six studies conducted PSA testing every 3 months,[5,8,14-17] 3 studies conducted PSA tests every 3 months for 1 year,[6,9,28] and 8 studies conducted PSA tests every 3 months for 2 years.[11,13,19,20,29-32] For studies following patients beyond 2 years, PSA testing was conducted every 6 months after the second year. Most included studies conducted a DRE as part of AS protocol. Sixteen studies conducted a DRE every 3 to 6 months.[5-9,12-16,18-22,29,32,33]

The studies reporting their active surveillance protocol conducted multicore (6- to 17-core) biopsies every 1 to 2 years.[5,10,12,15-18,21,23,28-30,33-35] Five studies conducted multicore biopsies every 2 to 4 years.[8,11,13,19,32] Regarding Multiparametric MRI, it has been shown to be a good predictor of disease reclassification.[36,37] Multiparametric MRI also had a negative predictive value of 83% to 100%[38] in one study that used transperineal template mapping saturation biopsy as a reference standard, and which included patients with a PSA range of 0.9 to 29 (median 7). One study also showed mpMRI to be a predictor of high-risk disease in the AS context.[37]

This recommendation is consistent with the active surveillance protocol presented in most of the studies reviewed for this guideline. Since most studies employed PSA testing,

DRE, and biopsy, these can be considered the three most important components of an active surveillance protocol. Although many studies reviewed here followed a repeat biopsy frequency of 1 to 2 years in their active surveillance protocol, the study with the most mature cohort of patients undergoing active surveillance[13] and two other studies opted for a repeat biopsy frequency of 2 to 4 years[8,11] and found similarly high prostate-cancer survival rates of 97% to 100%. Current evidence shows that PSA kinetics does not reliably predict disease stability or reclassification to higher risk state. Decisions about frequency of biopsy need to take into consideration individual patient factors including age, risk of progression, and comorbidities. The repeat biopsy frequency recommendation of a minimum of once every 3 to 5 years is based on the series reported by Klotz and colleagues,[39] which included 450 patients on active surveillance with a median follow-up of 6.8 years (range: 1–13). Overall survival rate was 78.6%. The 10-year prostate cancer actuarial survival rate was 97.2%. Compared with shorter repeat biopsy intervals, this recommended frequency potentially reduces the risk of complications that are associated with TRUS biopsy, including urosepsis,[40,41] without negatively affecting outcomes. A shorter interval between biopsies may be reasonable in selected patients and should be at the discretion of the ordering physician in consultation with the patient. Serial biopsy should not continue past the age of 80.

The role of MRI in active surveillance is evolving. Prospective multicentre trials reporting utility of MRI on entrance into active surveillance or in reclassification of disease risk are lacking. Single-centre publications looking at all men undergoing biopsy have found that mpMRI can reclassify patients when combined with systematic biopsy by identifying tumour targets missed with systematic biopsy.[38] mpMRI is useful in identifying anterior and higher volume tumours, and it is good in identifying findings that predict disease reclassification.[36,37] It is unclear whether this should be done on all patients or only on those in whom there is discordance between clinical findings, such as PSA and DRE. However, being cognizant of both the high cost of mpMRI and its promise, it is recommended that when a patient's clinical findings are discordant with the pathologic findings, a mpMRI is indicated. When indicated, it may be considered at entry or during follow-up. Discordant findings between a patient's clinical course and pathologic findings can include rapidly rising PSA, PSA density over 0.2, higher PSA than expected for prostate size, DRE abnormality, and very low PSA free/total ratio. The presence of these findings requires further investigation with mpMRI or earlier repeat biopsy.

## Recommendation 4

**RECOMMENDATION 4:** Daily 5-alpha reductase inhibitors may have a role in men on AS.

### Key evidence and qualifying statement for recommendation 4

Dutasteride is the only 5ARI that has been tested in an RCT. Evidence from a high-quality RCT detected a benefit for dutasteride administered to patients undergoing AS. In men with very low-risk prostate cancer undergoing AS and followed for 3 years, daily dutasteride delayed disease reclassification (hazard ratio [HR], 0.62; confidence interval [CI], 0.43–0.89) and improved quality of life at 18 months.[28] However, it should be noted that the RCT had short follow-up of 3 years and detected no difference between groups in survival rate outcomes. The Expert Panel believes that the evidence likely demonstrates a drug class effect; therefore finasteride may also have a role in men on AS. While the US Food and Drug Administration (FDA) has issued a warning about a possible low but increased risk for high-grade prostate cancer with the use of 5ARIs based on two RCTs that did not meet inclusion criteria for this guideline,[42] it is the opinion of the Expert Panel members that the benefits of 5ARIs outweigh the risks. 5ARIs can be prescribed to a patient undergoing AS as long as he is adequately informed about the risk and benefits of treatment. This is consistent with the Canadian Consensus Conference statement.[43]

## Recommendation 5

**RECOMMENDATION 5:** For patients undergoing AS who are reclassified to a higher risk category, defined by repeat biopsy showing Gleason score $\geq$7 and/or significant increases in the volume of Gleason 6 tumour, consideration should be given to active therapy (e.g., RP or RT).

### Key evidence and qualifying statement for recommendation 5

Based on RCTs of treatment versus observation, patients who benefitted most from therapy had Gleason 7 and higher prostate cancer volume.[20,44] Gleason score is a widely used disease classification measure and biopsy is the gold standard for measuring the status of disease. Thus Gleason 7 (4+3 pattern or 3+4 with Gleason pattern 4 pathology accounting for >10% total tumour) is the recommended indicator for disease reclassification to higher risk in prostate cancer. The most commonly reported active treatments received by patients on AS who were reclassified to higher risk were RP and RT.[5-7,9-13,21,45] Although clear biopsy criteria for defining progression of high volume Gleason 6 disease have not been established, it is the consensus of the Expert Panel that increasing volume of Gleason 6 tumour is an indicator of disease progression and of the need to consider active treatment. It is the consensus of the members of the Expert Panel that patients on AS with Gleason 7 disease on repeat biopsy can be considered for continued AS provided that Gleason pattern 4 accounts for ≤10% of total tumour. Prospective

intradepartmental consultation should be encouraged as an important quality assurance activity for Gleason score interpretation.[27] An RCT comparing RP to watchful waiting found that RP reduced the risk of distant metastases and reduced prostate cancer mortality rates.[44] In 6 studies, 17% to 31% of patients undergoing AS were reclassified to a higher risk group over time.[8-15,45] In 11 studies, 14% to 42% of patients undergoing AS received active treatment because of disease reclassification to higher risk, anxiety, patient choice, or another reason.[5-13,19,45] Since evidence to predict disease reclassification in prostate cancer was conflicting for PSA level and lacking for DRE and prostate cancer antigen3 (PCA3) level, these were not included in the recommendation. This recommendation is based on a consensus of opinion of the Expert Panel members.

## Further qualifying statements

Although one correlational study detected that patients from multidisciplinary clinics were more likely to receive AS than patients under the care of individual practitioners,[46] there is insufficient evidence to address the factors affecting the offer of, acceptance of, and adherence to AS. There is also insufficient evidence to make recommendations with regard to the personnel who should be responsible for the management of AS protocols. However, patients should have access to a multidisciplinary consultative approach when a change to active treatment is considered.

## Discussion

AS has become a commonly offered management strategy for patients with localized prostate cancer. In the systematic review for this guideline, no consistent protocol was found across the studies identified. There was also a lack of a standardized approach to identify appropriate candidates for AS. This guideline was undertaken to address these issues. Most included studies included PSA testing, DRE, and multicore repeat prostate biopsies in the AS protocol; however, the frequency of these tests varied significantly between studies. The development of an AS protocol should take into account the measures that can predict disease progression or reclassification. There was conflicting evidence whether PSA is a good predictor of disease progression or reclassification. Differences were also found in the ability of different measures of PSA, such as PSA velocity, PSA density, and PSA doubling time for predicting progression or reclassification.[9,11,30,31,37,47,48] PSA monitoring is considered a necessary component of an AS protocol, but a rising PSA may be best viewed as a trigger for reappraisal (e.g., MRI, repeat biopsy) rather than a trigger for intervention. MRI had a high yield in predicting disease reclassification; however, this is based on limited evidence.[36] The expert panel feels that the role of MRI in AS protocols will increase as new evidence becomes available; however, current evidence is not sufficient to recommend MRI in all cases.

This systematic review did not find RCTs comparing AS with immediate active treatments (e.g., RP, RT, HT) for prostate cancer. Most included studies were non-comparative. From a methodological perspective, this means that the quality of existing evidence is considered poor. This is the major limitation of the guideline. The lack of comparative studies, such as randomized controlled trials (RCTs) on AS, may be attributed to the slow progressive nature of prostate cancer, which would give such studies a very long maturation time. Another contributing reason is the difficulty accruing patients to RCTs, as demonstrated in the START trial (clinicaltrials.gov ID: NCT00499174) that was terminated early due to insufficient accrual. Many patients were unwilling to be randomized because of physician and patient biases, based on the non-comparative evidence in favour of AS and to avoid harms from possible overtreatment.

Congruent with a recent review,[2] survival rate outcomes from the studies included in this review indicated that prostate cancer mortality in AS cohorts is rare and men are more likely to die of other causes. The most common active treatments that AS patients received were RP, RT, and HT. Compared with immediate RP, AS patients who subsequently had delayed RP were more likely to have Gleason score upgrading; however, other post-RP outcomes did not significantly differ between groups. This suggests that there is acceptable low risk associated with undergoing AS and waiting to have RP or RT, further supporting an AS management strategy for patients with low-risk prostate cancer. While our review found an absence of evidence demonstrating superior oncologic outcomes in favour of AS, there was also no evidence of increased harm with AS compared to active therapies. This additional benefit of avoidance of harms has contributed to the widespread use of AS and to the recommendations in this guideline.

## Conclusions

In response to established concerns of overdiagnosis and potential harms from overtreatment of low-risk and some cases of intermediate-risk prostate cancer, AS has become a commonly recommended management strategy. It is important to develop evidence-based recommendations for a standardized protocol that can be applied consistently. Although high quality guiding evidence does not yet exist, due to the nature of prostate cancer as a slow progressive disease and to AS being a management strategy with few adverse events, the evidence is sufficient to make recommendations.

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