Updated evidence-based recommendations for cervical cancer screening in France
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Introduction  A national organized cytology-based cervical cancer screening program was launched in 2018 and rollout is ongoing. Concomitantly, the High Authority for Health (HAS) recently assessed new evidence on primary HPV testing to update screening recommendations.

Methods  The HAS commissioned systematic reviews and meta-analyses to evaluate the effectiveness of primary HPV screening; accuracy of HPV testing on self-samples; effectiveness of self-sampling to reach underscreened women; and triage strategies to manage HPV-positive women. Recommendations developed by the HAS were reviewed by a multidisciplinary group.

Results  Compared with cytology screening, HPV screening is more sensitive to detect precancers but less specific. In women aged ≥30, if the test is negative, HPV screening greatly reduces the risk of developing precancer and cancer for at least 5 years. HPV testing, using validated PCR-based assays, is as sensitive and slightly less specific on self-samples than on clinician-taken samples. Self-sampling is more effective to reach underscreened women than sending invitations to have a specimen taken by a clinician. Two-time triage strategies ensure a sufficiently high risk if triage-positive to justify referral and low risk if triage-negative allowing release to routine screening.

Conclusions  The HAS recommends three-yearly cytology screening for women aged 25–29 and HPV screening for those aged 30–65 with an extension of the screening interval to 5 years if the HPV test is negative. Self-sampling should be offered to underscreened women aged ≥30. HPV-positive women should be triaged with cytology. Those with abnormal cytology should be referred for colposcopy and those with normal cytology re-tested for HPV 12 months later. Recommendations for implementation of HPV-based screening in the organized program are provided. European Journal of Cancer Prevention 31: 279–286 Copyright © 2019 The Author(s). Published by Wolters Kluwer Health, Inc.

Keywords: France, health technology assessment, human papillomavirus, recommendations, screening, uterine cervical neoplasms

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Background

In 2018, there were an estimated 2920 new cases of cervical cancer and 1120 deaths from it in mainland France (Defossez \textit{et al.}, 2019). The incidence and mortality of cervical cancer have been declining over the past several decades, as in other high-income countries (Karim-Kos \textit{et al.}, 2008; Arbyn \textit{et al.}, 2009). This has been attributed to the widespread use of cervical cytology screening (IARC, 2005). However, these reductions have slowed since 2005.

Apart from some locally organized programs in a few departments (Hamers \textit{et al.}, 2018), cervical screening in France was mostly opportunistic until quite recently. In 2010, the French National Authority for Health (HAS) recommended the implementation of a population-based organized cervical screening program (HAS, 2010). Three-yearly cervical cytology for women aged 25–65 years was the recommended screening method. At that time, there was insufficient evidence to recommend the human papillomavirus (HPV) test as a primary screening method, and having an organized cervical cancer screening program was deemed necessary before primary HPV screening could be considered. In 2016, the French National Cancer Institute issued guidance for clinical management of abnormal cervical cytology (INCa, 2016). In 2018, a nationwide population-based organized screening program was launched and rollout is currently ongoing. It aims at increasing screening coverage to 80%, reducing inequalities in access to screening and decreasing cervical cancer incidence and mortality by 30% within 10 years (République française, 2014). While the invitation strategy excludes women recently screened opportunistically, the program is designed for the entire target population of asymptomatic women aged 25–65 years and includes all screened women – opportunistically or following invitations. The 3-year coverage for cervical screening with cytology for the period 2015–2017, prior to the launching of the organized program, was 59% (Hamers and Jezeweski-Serra, 2019).
The recognition of the strong causal relationship between persistent cervical infection with high-risk HPV (hrHPV) types and occurrence of cervical cancer (Bosch et al., 2002) has led to the development of a series of HPV tests to detect nucleic acid of the virus. The detection of hrHPV is considered to be potentially useful as a primary screening test (von Karsa et al., 2015) and international criteria for hrHPV tests for primary screening use have been described (Meijer et al., 2009). HAS has recently assessed new evidence on the use of HPV testing in primary cervical cancer screening to update the national recommendations. The objective of this paper is to provide a summary of the literature review and to explain how the recommendations were made on the level of evidence that could be derived from systematic reviews and meta-analyses.

Methods
Scoping and question generation
The main stakeholders were consulted to identify a list of key issues to be addressed (see Box 1). These constituted the starting point for developing research questions.

Neither the test accuracy nor the effectiveness of cytology for cervical cancer screening was reviewed as those had been established previously (Arbyn et al., 2010; HAS, 2010). The evidence review addressed also the age for starting screening with HPV test and the screening interval. Cost-effectiveness of cervical cancer screening in France comparing screening with HPV testing and cytological screening was evaluated previously by the French National Cancer Institute (Barre et al., 2017) and was not reassessed in the current evaluation. The role of co-testing (systematic use of both cytology and HPV test) was not considered as the potential benefit of co-testing versus HPV test alone is extremely small and this strategy has been shown to be inefficient (Arbyn et al., 2012; Schiffman et al., 2018).

Scientific evidence retrieval and synthesis
HAS commissioned the Belgian institute for health, Sciensano, to conduct systematic literature reviews and meta-analyses to investigate the scientific evidence of specific questions related to the key issues (1) to (4) (see Box 1). The detailed methodology for the scientific evidence review is described in an annex of the HAS scientific report (HAS, 2019), which is available from the second author (A.P.) upon request (a.poulle@has-sante.fr). The evaluation of HPV testing on self-samples was published in 2018 (Arbyn et al., 2018). The questions were disentangled into participants, interventions, comparisons, outcomes and study design (PICO) components. Pubmed-Medline, Embase and the Cochrane Library were searched until 15 April 2018. Diagnostic accuracy questions were assessed taking into account the STARD guidelines (Bossuyt et al., 2003) and using the QUADAS checklist (Whiting et al., 2003; Whiting et al., 2011) to evaluate the quality and design of included studies. Efficacy questions were addressed using the CONSORT framework (Moher et al., 2001) and the Cochrane tool for assessing the risk of bias in randomized trials (Higgins et al., 2011). The meta-analyses followed PRISMA guidelines for reporting of meta-analyses, and recommendations established by The Cochrane Collaboration for diagnostic test accuracy and intervention trials (Deeks et al., 2010; Moher et al., 2009). Random-effects models were used for computing pooled estimates.

The higher sensitivity for precancers of hrHPV-based screening compared to cytology screening is associated with a drop in specificity, which may result in a decreased cross-sectional positive predictive value (PPV) and may lead to unnecessary follow-up and overtreatment of screen-positive women, in particular in women younger than 30 years. Hence, the triage of women with a positive hrHPV test is an important clinical issue to address. A risk-based approach was used to evaluate triage algorithms of HPV-screened positive women (Wentzensen et al., 2016; Arbyn et al., 2017). The risk of precancer (cervical intraepithelial neoplasia grade 3 or worse disease [CIN3+]) for women with a positive triage result (=PPV) and for those with a negative triage result (complement of the negative predictive value [cNPV] = 1 − NPV) and the proportion of triage-positive women, that will be referred for colposcopy was computed using three hypothetical background situations: (1) lower risk group where the average risk of CIN3+ prior to triage is 5%; (2) medium group with a CIN3+ risk of 9%; and (3) higher risk group with CIN3+ risk of 15%. Pretest-posttest probability plots were constructed to help evaluate the utility of triage strategies. A strategy was considered acceptable when the posttest risk of CIN3+ in case of a positive triage (PPV) exceeds 10% and when this risk is lower than 1% in case of a negative triage (cNPV).

Contextual evidence
A narrative review of the gray and published literature was done to provide an overview of experiences in countries that recently switched to HPV-based screening or plan to do so. Issues related to the integration of HPV-based within the national organized screening program were mostly based on the opinion of the working group members, described in the HAS evaluation report (HAS, 2019). The question on whether screening strategy should be adapted according to HPV vaccination status was handled by reviewing policies and recommendations in other countries and considering the low vaccination coverage in France (Fonteneau et al., 2019).

Evidence appraisal and formulation of recommendations
A working group of experts in obstetrics and gynecology, pathology, virology, general practice medicine,
public health and health economics was convened by HAS. The working group was asked to appraise and interpret the scientific evidence considering the overall balance of risks and benefits and to provide inputs on feasibility, implementation and other informal evidence. Recommendations were drafted by HAS and reviewed and approved by the working group before submission to review by a larger group of experts and stakeholders.

Box 1. Key issues and related specific research questions to be addressed

(1) What is the role of hrHPV testing in primary screening for cervical cancer?
- What is the diagnostic accuracy of the hrHPV test compared to cytology in primary cervical cancer screening to detect cervical precancer?
- What is the efficacy of HPV-based compared to cytology-based screening to prevent cervical precancer and cancer?

(2) What is the role of self-sampling for HPV-based cervical cancer screening?
- What is the diagnostic accuracy of hrHPV testing on vaginal self-sampled versus on cervical clinician-taken samples?
- What is the efficacy of offering vaginal self-sampling kits to reach underscreened women compared to sending invitation or reminder letters?

(3) What are the optimal triage algorithms to manage women with a positive HPV screening test?
- What is the best test or combination of tests which results in the highest sensitivity for cervical precancer and lowest burden of follow-up?

(4) What is the role of the p16 or p16/Ki67 molecular markers in primary screening?
- What is the diagnostic accuracy of p16 or p16/Ki67 compared to cytology or hrHPV test in primary cervical cancer screening?

(5) Should the cervical cancer screening strategy differ according to HPV vaccination status?

(6) What are the organizational issues for the implementation of HPV-based screening in the national organized cervical cancer screening program?

Results

Evidence summary

What is the diagnostic accuracy of the hrHPV test compared to cytology in primary cervical cancer screening to detect cervical precancer?

Previous diagnostic test accuracy meta-analyses (Arbyn et al., 2012; Koliopoulos et al., 2017), were updated with focus on new RCTs conducted in high-income countries (the Canadian FOCAL (Ogilvie et al., 2018) and the Australian COMPASS (Canfell et al., 2017) trials), demonstrating higher sensitivity of hrHPV testing than cervical cytology to detect cervical precancer (CIN2+ and CIN3+) (Table 1).

However, a higher cross-sectional sensitivity of hrHPV testing for detecting CIN2+ and CIN3+ does not provide sufficient evidence to assume that HPV-based screening will decrease the incidence of cervical cancer more than cytology-based screening. Indeed, CIN2 and even CIN3 lesions can regress without treatment (Ostor, 1993; Tainio et al., 2018) and it cannot be excluded from cross-sectional findings that HPV tests may just pick up a more regressive disease. To prove that more progressive lesions are detected by hrHPV testing, it must be demonstrated that women with a negative screening test have a lower incidence of precancer or cancer by screening with HPV testing compared to screening with cytology. Evaluating the efficacy of screening requires a longitudinal (preferentially randomized) design to assess for the reduction in disease.

What is the efficacy of HPV-based compared to cytology-based screening to prevent cervical precancer and cancer?

The updated systematic review of six RCTs comparing cytology with HPV-based included the Canadian trial FOCAL (Ogilvic et al., 2018) and four European RCT conducted in Sweden (Sweedishscreen), England (ARTISTIC), Italy (NTTTC phase I) and the Netherlands (POBASCAM) (Naucler et al., 2007; Kitchener et al., 2009; Ronco et al., 2010; Rijkaart et al., 2012). The results confirm the compelling evidence that HPV-based screening results in a lower incidence of CIN3+ and of cervical cancer than screening with cytology among women that were baseline screen-negative (Table 1).

Table 1 Role of the hrHPV test in primary screening for cervical cancer screening: results of the evidence review to answer research questions related to key issue (1) (see Box 1)

| Outcome | No of RCTs | Detection rate ratio (95% CI) |
|---------|------------|-----------------------------|
| CIN2+   | 6          | 1.39 (1.23–1.57)            |
| CIN3+   | 5          | 1.28 (1.09–1.51)            |
| hrHPV test vs. CC |            |                             |
| CIN2+   | 3          | 1.44 (0.87–2.39)            |
| CIN3+   | 3          | 1.47 (0.75–2.88)            |

Diagnostic accuracy of the hrHPV test compared to cytology in primary cervical cancer screening to detect cervical precancer

Efficacy of HPV-based compared to cytology-based screening to prevent cervical precancer and cancer

| Outcome | No of RCTs | Relative sensitivity (95% CI) |
|---------|------------|-----------------------------|
| CIN3+   | 5          | 0.39 (0.31–0.50)            |
| Cancer  | 4          | 0.21 (0.06–0.74)            |

CC, conventional cytology; CI, confidence interval; CIN, cervical intraepithelial neoplasia; CIN2+, CIN grade ≥2; CIN3+, CIN grade ≥3; HPV, human papillomavirus; hrHPV, high-risk HPV; LBC, liquid-based cytology; RCT, randomized controlled trial.
A pooled analysis of the individual patient data from the four above-mentioned European RCTs provided more details regarding the protection against invasive cervical cancer by HPV-based compared to cytology-based screening (Ronco et al., 2014). The main results were

- the protective effect became observable 2.5 years after screening (relative protection of 0.45 [95% confidence interval (CI), 0.25–0.81];
- the protective effect was similar for early (stage 1A) or advanced (stages ≥1A) cervical cancer;
- the protective effect was observed both in the total screened group (relative protection of 0.60 [95% CI, 0.40–0.89]) and in women with a negative screening test at baseline (relative protection of 0.30 [95% CI, 0.15–0.60]);
- there was no protective effect observed in the age group of <30 years (relative protection of 0.98 [95% CI, 0.19–5.20]);
- HPV-based screening protects more than cytology against adenocarcinoma (relative protection of 0.31 [95% CI, 0.14–0.69]) when compared to the protection against squamous carcinoma (relative protection of 0.78 [95% CI, 0.49–1.25]).

What is the diagnostic accuracy of hrHPV testing on vaginal self-sampled versus on cervical clinician-taken samples?

The meta-analysis included a total of 56 studies (Arbyn et al., 2014; Arbyn et al., 2018). High-risk HPV tests based on PCR were as sensitive on self-samples as on clinician samples to detect CIN2+ or CIN3+ (Table 2). However, hrHPV tests based on signal amplification were less sensitive on self-samples. The specificity to exclude CIN2+ was 2 or 4% lower on self-samples than on clinician samples, for hrHPV assays based on PCR or signal amplification, respectively.

| Type of hrHPV test | Outcome | No. of studies | Relative sensitivity (95% CI) | Relative specificity (95% CI) |
|--------------------|---------|----------------|-----------------------------|-------------------------------|
| SA-based hrHPV test | CIN2+ | 23 | 0.86 (0.60–0.89) | 0.96 (0.93–0.98) |
| CIN3+ | 9 | 0.86 (0.76–0.98) | 0.97 (0.95–0.98) |
| PCR-based hrHPV test | CIN2+ | 17 | 0.99 (0.97–1.02) | 0.98 (0.97–0.99) |
| CIN3+ | 8 | 0.99 (0.86–1.02) | 0.98 (0.97–0.99) |

What is the efficacy of offering vaginal self-sampling kits to reach underscreened women compared to sending invitation or reminder letters?

The meta-analysis of RCTs included a total of 25 participation trials (Verdoodt et al., 2015; Arbyn et al., 2018). The different trials used very different strategies to offer the self-sampling kits including mailing kits directly to women’s home address, opt-in where women had to request a sampling kit; community campaigns and door-to-door interventions. Mailing self-sample kits to the women’s home address resulted in a higher participation than invitation or reminder letters (Table 2). Opt-in strategies were generally not significantly more effective than invitation letters. Direct offer of self-sampling kits by health professionals to women in communities that were underscreened generated high participation rates (>75%); these studies were conducted in resource-constrained settings.

The adherence to follow-up was statistically significantly lower in women who tested positive for hrHPV in the self-sampling arm versus women in the control arm in the trials in which follow-up adherence was reported in both arms (relative adherence of 0.91 [95% CI, 0.80–1.04]). The rate of CIN 2+ detected per 1000 women was 2.8 times higher (95% CI, 1.44–3.61) in the self-sampling arms than in the control arms.

What is the best test or combination of tests which results in the highest sensitivity for cervical precancer and lowest burden of follow up?

The review aimed at identifying triage testing with biomarkers (HPV16 and 16/18 genotyping, p16, p16/Ki67) and repetition of hrHPV-DNA testing, cytology and/or combinations thereof which results in the highest sensitivity for cervical precancer at the lowest burden of follow-up. Diverse triage strategies were available in 59 identified studies on clinician collected samples, ranging from one-step to two-step triage strategies with diverse methods such as cytology, repeat hrHPV testing, HPV genotyping and/or p16 or p16/Ki67 immunohistochemistry. A total of 29 strategies (reported in 51 studies) to triage women HPV positive on a clinician-taken sample and 20 strategies (reported in 10 studies) to triage women HPV positive on a self-sample were retrieved. The pooled sensitivity and specificity of the identified triage strategies to identify CIN2+ and CIN3+ precancerous lesions were computed.

The triage strategy that was best documented – in 26 studies – is reflex cytology triage at cut-off atypical squamous cells of undetermined significance (ASC-US),
meaning that women with ASC-US or more severe lesions on cytology are referred for colposcopy and further investigations if needed whereas women with negative cytology return to routine HPV screening 5 years later (Table 3). The sensitivity of this strategy is considered to be too low to safely allow negative women to return to routine screening. Adding a second, delayed triage step for women who had a negative cytology triage increased the sensitivity but also decreased the specificity.

In a hrHPV-positive population with a pretriage intermediate underlying background risk of CIN3+, a two-step triage strategy with twice cytology (reflex cytology at the time of screening followed by second cytology 6–12 months later if the first cytology was negative) at cut-off ASC-US offers a good balance between efficiency (four to nine referrals to detect one CIN3+, ~40% of referrals) and safety (risk of CIN3+ in triage-negative women of 0.5–0.9%). If the background risk is higher, the safety becomes borderline (risk of CIN3+ in next 3–5 years of 1.4%). The safety of two-step triage strategy can be increased by adding HPV16 or HPV16/18 genotyping and/or hrHPV testing (=co-testing at triage) or by replacing cytology with a repeat hrHPV test. In these scenarios, safety criteria are obviously fulfilled, even when the background risk is high, but referral rate is high (67 to 71%).

A two-step triage strategy with twice cytology (reflex cytology at the time of screening followed by a second cytology 6–12 months later if the first cytology was negative at cut-off ASC-US yielded acceptable results in low- and medium-risk situations, and borderline safety in a high-risk situation. ASC-US reflex cytology followed by delayed hrHPV testing with or without cytology one year later was also satisfactory in medium- and high-risk situations but was less efficient (PPV <10%), in a low-risk situation.

**What is the diagnostic accuracy of p16 or p16/Ki67 compared to cytology or hrHPV test in primary cervical cancer screening?**

In total, three studies were included. These studies assessed overexpression of the p16 protein by an anti-p16 ELISA assay, or by a double immunostaining on p16 and Ki67. Testing with p16/Ki67 showed good cross-sectional specificity but lower sensitivity for cervical precancer compared to HPV screening. More data regarding longitudinal safety are needed.

**Recommendations**

Based on the review of the scientific and contextual evidence, HAS updated its recommendations on cervical cancer screening. The main messages are listed in Box 2. For the full recommendation statement, please see the HAS report (HAS, 2019).

**Box 2. Recommendations for cervical cancer screening: main messages**

The recommendations concern asymptomatic women who have a cervix (who have not had a hysterectomy with removal of the cervix) and are aged 25–65 years.

In the current state of knowledge, the screening procedure should be the same for HPV-vaccinated and unvaccinated women.

**Screening methods, age, interval and management of women screened HPV-positive**

- For women aged 25–29 years, screening recommendations remain unchanged. Women should be screened with cytology every 3 years, as previously recommended. Liquid-based cytology should be used. Women with abnormal cervical cytology should be managed according to existing guidelines produced by the French National Cancer Institute.
- Women aged 30–65 years should be screened with hrHPV testing as the primary screening test, at a 5-year screening interval.
- hrHPV testing on vaginal self-sampling is an alternative to hrHPV testing on clinician collected cervical samples for some women. Self-sampling should be offered to underscreened women from the age of 30 years.
- Women who have a hrHPV-positive test on screening should be managed using a two-step triage strategy. The first step is a reflex cytology, thus performed at the time of screening on the specimen collected for screening. If the cytology result is ASC-US or more severe abnormalities, the woman should be referred to colposcopy. If the cytology is negative, the women should be called 12 months later for a repeat HPV test.
with colposcopy referral if HPV-positive and return to routine screening 5 years later if HPV-negative.

**Implementation of HPV-based screening in the national organized cancer screening program**

- Quality control should be set up for HPV testing. Compliance with screening recommendations by clinicians and labs should be monitored. Only assays that are clinically validated for use in cervical cancer screening should be used. Consideration should be given to tender procedures for supplying hrHPV tests across the country.
- Healthcare providers should ensure that screening tests (cytology or HPV test) are offered in accordance with recommendations regarding women’s age and screening interval.
- To enable women to make an informed choice about screening, information materials and communication actions on HPV screening for women and for health care professionals should be developed.
- As it is the case for cervical screening with cytology, HPV test should be fully reimbursed every 5 years for women aged 30–65 years.

**Discussion**

Following other countries in Europe and elsewhere (Lew et al., 2017; CADTH, 2019; American Cancer Society, 2020; Maver and Poljak, 2020), France has also recommended the use of the HPV test as the primary cervical cancer screening method, in July 2019. A year later, in July 2020, these recommendations were officially integrated into the national population-based cervical cancer screening program through a ministerial order (Ministère des Solidarités et de la santé, 2020) and a guidance for program evaluation, including performance indicators, was produced (Santé publique France, 2020).

The transition to complete rollout of HPV primary screening may be long and complex. For instance, in the Netherlands, the first European country that introduced HPV primary screening, in 2017, the new program started only after a preparation phase of more than 4 years. The implementation of HPV primary screening is now being rolled out in France. However, as in most countries, the onset of the COVID-19 pandemic in early 2020 led to a scaling down of cancer screening activities (Richards et al., 2020), which may result in delaying complete HPV screening rollout.

A switch to HPV testing constitutes a major operational and culture shift for clinicians, women, and laboratories (CADTH, 2019). Acceptance of this new screening test (i.e. sexually transmitted infection) may be challenging. Preventing a potential drop in screening and providing easily accessible information and education material to the public and to clinician are important.

A list of clinically validated tests for HPV-based cervical cancer screening, based on the Meier criteria, was produced in 2015 (Arbyn et al., 2015). As evidence accrues, the validation principles and the list of tests need updating.

One major issue is the change in laboratory configuration, workflow and human resources. The cervical cytology workload is expected to decrease substantially, which will likely result in job or revenue losses for cytopathologists. However, cytology as a triage test for HPV-positive samples remains key in the screening process. Staff reconversion while ensuring that expertise is kept and that a sufficient number of staff will embrace a career path that may no longer appear attractive will be a challenge. Because of the lower specificity of primary HPV screening compared to cytology screening, the number of colposcopy referrals is expected to increase.

Nonattendance is a concern with existing cervical cancer screening programs. Besides high efficacy, HPV testing has the additional advantage that it can be performed on self-collected vaginal samples and studies have shown that providing self-sampling kits improves participation of underscreened women. Modalities for offering self-sampling in France still have to be defined.

Most HPV infections clear spontaneously. Only a small proportion of HPV infections persist and, eventually, may develop into CIN3+ (Schiffman et al., 2007). Hence, appropriate triage testing, management and follow-up of HPV-positive women are of critical importance in optimizing the balance of benefits and harms for primary HPV screening. However, there is no consensus on the optimal management of HPV-positive women. Triage strategies were considered acceptable when the PPV (risk of CIN 3+ when the triage was positive) was greater than 10% and the cNPV (risk of CIN 3+ when screening was negative) was lower than 1%. There are no universal thresholds and it is up to each country to define acceptable thresholds (Arbyn et al., 2017).

Compliance of HPV-positive women to triage is a major challenge. Two-step triage strategies are characterized by a certain degree of drop-out of women under follow-up. Triage of women with HPV-positive on a self-collected sample is a further challenge because these women, often hard to reach, must be referred to a clinician for cytopathological cervical sampling. Emerging molecular markers which may be useful in triage of HPV-positive women are being developed, including extended genotyping, methylation markers, expression of oncoproteins such as E6 and E7, viral mRNA testing, evolution of type-specific viral load.

In the future, these may provide alternatives for the currently recommended triage strategy. Ideally one would aim at a one-step triage using tests that could be performed on self-samples.
Conclusion
These recommendations constitute a milestone towards the elimination of cervical cancer in France. Population-based information must be established to monitor and evaluate their implementation. Screening program performance indicators including participation, adherence, quality and impact should be published regularly.

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